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## Announcement

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The next number of the MEDICAL CLINICS OF NORTH AMERICA, now in preparation and to be published shortly, will be devoted to the work that has been done at several of the Base Hospitals at the various camps. This number is being brought out with the co-operation of the Surgeon General's Office in Washington. The first article, "Clinical Research in United States Army Base Hospitals," will be by Surgeon General Gorgas.

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# THE MEDICAL CLINICS OF NORTH AMERICA

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VOLUME 2

NUMBER 1

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CLINICAL LECTURE BY DR. FRANK S. MEARA

AT CORNELL UNIVERSITY MEDICAL COLLEGE

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## HYPERPIESIA OF CLIFFORD ALLBUTT (ESSENTIAL HYPERTENSION)

Differentiation from Interstitial Nephritis and Arteriosclerosis  
Possibility of Mistaking End-products of Hypertension. Pioneer  
Work in Division of Groups. Theodore Janeway's Subdivision  
of Hypertensive States. Division of Alfred Stengel. Disease  
Entity of Clifford Allbutt, Hyperpiesia, Essential Features,  
Course, End-results, Age Incidence, Early and Late Manifesta-  
tions, Therapy, Prognosis Contrasting Cases

WHEN a patient offers the history of a long standing high blood pressure he will be pronounced almost inevitably a case of chronic Bright's disease or of arteriosclerosis. This diagnosis will be in accordance with the generally accepted instruction of the last generation.

If the patient's urine shows traces of albumin and casts, hyaline or granular, the diagnosis will be chronic Bright's unless the physician, shrinking from pronouncing the doom of the patient or puzzled at the apparent well being of a man or woman entertaining so dire a condition, is led to call it chronic interstitial nephritis, although he knows authority would charge him with making a discrimination without a difference, still he feels a vague comforting difference in this discrimination.

If the urine of the patient with chronic hypertension is innocent of any deviation from the normal, or if the attention of the

physician is fixed by marked thickening of palpable arteries, or the patient has had apoplectic attacks, major or minor, he will be considered a case of arteriosclerosis. And so, indeed, he is. But the diagnosis carries with it in the mind of the diagnostician the connotation that the arteriosclerosis was the essential and causative factor in the whole disturbance, which it is not. By the more careless the hypertension may be overlooked entirely and the diagnosis established in terms of the end-products of the process, cardiac disease or apoplexy.

The observant clinician soon noted that there were not a few cases that did not fit well into either one or the other groups into which chronic hypertensive cases were divided. Cases that should fit snugly into the frame labeled chronic Bright's disease failed to show any of the urinary findings considered essential to Bright's disease, and it became necessary to conceive of these as in the prealbuminuric stage of Bright's disease (Mahomed). Cases that ought to fall under the category of arteriosclerosis failed to demonstrate any palpable or visible artery in a sclerotic condition, so the term "latent arteriosclerosis" (Von Basch) was coined, meaning thereby that an arteriosclerosis did actually obtain in a vessel or group of vessels which play a rôle in the maintenance of a normal blood-pressure—e g, the splanchnic vessels or perhaps the cerebral vessels—while others imagined a presclerotic stage in the production of arteriosclerosis (Huchard). This latter conception was pioneer work that thinned the woods.

Students of the subject in our own country were illy satisfied with the old division. Theodore Janeway, studying the rich material of his father's private practice and his own, felt the necessity of splitting off another group which he termed "chronic hypertensive cardiovascular disease," a name as good as another for what I am about to describe. I would recommend to you these studies of Dr Janeway on hypertensive states.

My own attention was first called to this group, distinct from Bright's or arteriosclerosis as I had visualized them, by Dr Alfred Stengel,<sup>1</sup> who described vividly a group of hypertensive cases standing in striking contrast to the companion picture he

<sup>1</sup> Jour Amer Med Assoc., October 24, 1914, p 1463

drew of primary interstitial nephritis This group became clearer cut as they multiplied upon my files Its position as a distinct disease entity we owe to Clifford Allbutt, Regius Professor of Physic in the University of Cambridge, England, more than to any other man. A lifelong student of cardiovascular disease and a prolific contributor to the literature on the subject, he gathered together the abundant but scattered data on the subject in a veritable *magnum opus* published in 1915 under the title of "Diseases of the Arteries including Angina Pectoris," in which it appeared under the designation of "Hyperpiesia "

By hyperpiesia he defined a state, condition, or disease whose essential feature and earliest manifestation is hyperpiesis or elevated blood pressure. It is the condition sometimes referred to as essential or primary hypertension, and is the group designated by Janeway as "chronic hypertensive cardiovascular disease" In the first number of these CLINICS Mosenthal and Hamman each discussed this entity

The cause of the heightened blood pressure is not yet known. In the course of time it is followed by cardiac hypertrophy and by arteriosclerosis It is essentially chronic in its course The end-result is either cardiac failure or an arterial accident, cerebral or coronary, in the vast majority of cases, and the patients rarely, if ever (and it is my experience, never), die of uremia.

Observe these salient features of the condition. It occurs especially in people of apparently robust health. For months or, rather, for years neither they nor their friends suspect aught is wrong with their health These patients are usually of ruddy complexion, stocky build, plethoric habits, active temperament, live men and women. To them more than to others your greeting of "How well you look!" rings with conviction. These people enjoy life and the good things of life. They are endowed with hearty appetites and indulge them freely They are gourmets rather than gormands, though often fairly earning the latter title. They are not heavy drinkers, as a rule, but often use alcohol to add to the pleasures of the table There are, however, many exceptions to these statements

When symptoms occur that elicit the attention and concern

of the patient, the hyperpiesis has obtained for a long period of time—years. Most of these patients are, at the time of the development of their symptoms, in late middle life, a decade older than the true Bright's, primary interstitial nephritis, which occurs in early middle life, and a decade younger than the cases of senile arteriosclerosis, senile myocarditis, or cardio-sclerosis and arterosclerotic kidney.

Life insurance examinations, however, and the routine use of the sphygmomanometer bring to us the fact that this condition begins, certainly in a large percentage of the cases, if not in the majority, in early middle life. The earliest symptoms noted are increasing dyspnea on exertion, marking the beginning break in cardiac compensation, or precordial pain or a sudden onset of pulmonary edema, or the first symptoms are referable to the cerebral vessels, slight shocks or warnings of their early advent, or it may be increasing nervousness, irritability, fatigue, and loss of concentration. But now the process is far advanced. Insidiously the cause has been operative for years, and nobly and efficiently the heart has responded to ever-increasing demands and made no appeal for help. I shall cite to you a typical case.

Mrs F H, fifty-one years of age, became aware of high blood-pressure two years ago. The reading was 230 m.m Hg in systole, and has hovered about that figure since unless the patient is kept some time in bed, when it falls somewhat. A year later she had a cerebral accident characterized by mental confusion, difficulty of speech, and some numbness in the right arm. This cleared up fairly quickly. After an interval of another year she had a repetition of aphasia, which now, after two weeks, is still obvious in her hesitation in choice of words. The patient is thick-set, a well-developed woman of firm tissues and *florid complexion*. The pupils react to light and accommodation. The *eye-grounds show tortuous veins, small arteries, and, near either disk, a small hemorrhage*. The heart is moderately hypertrophied. The right border is 3 cm from the midsternum in the fourth space, and the apex is 10½ cm from the midsternum in the fifth space. Apex is a little thrusting,

sounds of good quality, no murmurs, no arrhythmia    *Blood-pressure* 200/120    *Wassermann* is negative.

*Renal Functions* —The *concentration tests* (Mosenthal) show a specific gravity varying from 1016 to 1030 and the twelve-hour night collection amounted to 565 c.c.

The *phenolsulphonephthalein test* gave an output of 65 per cent. of the dye in two hours

The *blood constituents* amounted to 1 mg of uric acid in 100 c.c., 18.5 mg of urea nitrogen in 100 c.c., 3.4 mg of creatinin in 100 c.c.

Urine showed a trace of albumin and no casts

It will be seen, then, that no test gave evidence of kidney impairment in a clinical sense. The trace of albumin and the very trivial nocturia are due to arteriosclerotic changes in the renal vessels, as will be later discussed

*Age* —As already stated, these cases are discovered in later middle life in the majority of cases, but are by no means confined to this period. Of 50 of my cases, the ages when observed by me were distributed by decades as follows

To 10 years	1 or 2 per cent.
10-20 "	0
20-30 "	0
30-40 "	2 or 4 "
40-50 "	20 or 40 "
50-60 "	14 or 28 "
60-70 "	7 or 14 "
70-80 "	6 or 12 "

56 per cent. fell between 45 to 55 years.

68 " " " 45 to 60 "

The youngest patient in this group, G F, was eight and one half years of age at the time of observation. He had had intense headaches since the age of five years. His blood pressure was 210/150, and yet, to the casual observer, he appeared in good health, had a high color, and was an active, energetic boy. The day before I saw him he carried off the honors in a battle royal in the street. His heart was much hypertrophied, the left border being 10 cm. from midsternum in the fifth space. Transitory edemas of the feet bespoke faltering compensation.

His eye-grounds showed arteriosclerosis of the retinal vessels, hemorrhage, and some exudate of the type of an arteriosclerotic retinitis

Urine examination was as follows Specific gravity 1010, heavy trace of albumin, and no casts Phthalein test gave 42 per cent the first hour, 21 per cent the second, total of 63 per cent, a normal figure His urea-nitrogen in the blood was 20 mg per 100 c c, a normal figure These tests were later repeated in the laboratory of St Luke's Hospital in this city, with practically identical results He had later a hematuria which was repeated, and two months later a hemorrhage from the bowel This was followed by a mesenteric thrombosis, a perforation of the intestine in two places, peritonitis, and death

It is understood, of course, that occurrence at so early an age is rare, but this case illustrates how catholic in its choice the affection may be Its incidence in old age is common enough, as my figures show, though in most instances it must be assumed that the trouble began a number of years before While a systolic pressure of 200 or a little less is common enough among patients seventy years or over, the excessively high pressures occur among those in later middle life

As I have said, many cases are discovered accidentally in the course of a routine examination, one, I recall, in a woman suffering from lumbago whose blood-pressure of 210/110 had never been suspected Once more I reiterate that the common diagnosis in these cases is Bright's disease, chronic interstitial nephritis, cardiorenal disease, with the implication that the kidney is profoundly altered both in structure and in function, especially is this so if attention has been attracted to the trace of albumin and to casts

Clinically, however, these cases are remote from Bright's disease As a rule, when the diagnosis is made, the patient is a decade older in hyperpiesia than in Bright's disease Again, when the diagnosis is made, cachexia is already noted in Bright's, it is a late phenomenon in hyperpiesia The course is a slow one, a relatively benign one in hyperpiesia, much more hurried and malignant in Bright's Most important of all, uremia is

not seen, or but rarely (in none of my cases), in hyperpiesia, it is the characteristic episode in Bright's Albuminuric retinitis occurs in Bright's and not in hyperpiesia. Finally, tests of renal function determine a decompensation in Bright's and a practically unimpaired function in hyperpiesia.

The pathologic histology of the kidney in hyperpiesia has not yet been sufficiently worked out. That many of the kidneys of long-standing hyperpiesia are profoundly altered in structure is not to be doubted. Many are small, shrunken, and have adherent capsules. Such kidneys have been classified as chronic interstitial nephritis, granular kidney, and conceived to be identical with the kidneys of clinical Bright's. Such terminal kidneys are so altered architecturally that able pathologists frankly acknowledge that the sequence of pathologic changes that eventuate in the shrunken kidney is obliterated in the process.

It is probable, in primary interstitial nephritis, the granular kidney of Bright's, that the early changes were inflammatory, with early implication of the intertubular and afferent vessels of the glomeruli with thrombosis, due to the unknown toxic substance that is responsible for the uremic manifestations, while in the kidneys of hyperpiesia the process is replacement of nobler tissue, parenchyma starved slowly by the insufficient blood-supply of the sclerotic renal vessels, by connective tissue, and never at any stage the seat of inflammation. It is entirely possible that all reserve tissue may be lost and the kidney wasted below the threshold of competency, but this is rare, and even then, I believe, gives rise to a set of symptoms different from uremia, unless we grant the so-called "chronic uremia," characterized by progressive stupor and coma, but not by twitchings, convulsions, or albuminuric retinitis.

Here is the history of a patient sent to me as a case of Bright's disease.

H. W. B. was fifty-six years of age, a business man. His hypertension was first noticed three to four years previous, that is, at the age of fifty. His blood pressure when I saw him was 210/110 and his urine had a specific gravity of 1022, showed a



faint trace of albumin, and a few hyaline casts. On the basis of his hypertension and urinary findings the diagnosis of Bright's disease had been established.

His heart was much hypertrophied, the lower border  $16\frac{1}{2}$  cm from midsternum in the fifth space, and there was a faint systolic murmur over the second right space attributable to an atheromatous aorta. His palpable arteries were thickened, but the retinal vessels and the eye-grounds were unchanged.

Renal tests were as follows:

Concentration test, 2-hour portions varying from 17 to 66 c.c., showed a specific gravity of 1021 to 1034 (normal), night urine 520 c.c. (very slight nocturia), phthalein, 44 plus 16 equals 60 in two hours (normal).

Blood constituents: Uric acid, 2.8 mg per 100 c.c., urea nitrogen, 16.5 mg per 100 c.c., creatinin, 4.5 mg per 100 c.c.

Repeated by another chemist on another occasion: Uric acid, 2.1, urea-nitrogen, 24.0, creatinin, 0.2.

All of these are normal and agree, except the creatinin, the most difficult to determine by the colorimetric method. Once he had had an attack of cardiac insufficiency, coming on abruptly. He had never had symptoms referable to his kidneys.

Here, then, we have a typical case of hyperpiesia, living under the sword of Damocles in the shape of uremia. Some of these cases, however, have had a history of nephritis in the past, among my patients most commonly during a pregnancy. It is a nice question to answer whether we are dealing with a contracted kidney, secondary to an acute productive nephritis of pregnancy, or with a hyperpiesia in a woman who had a nephritis from which she recovered, or both conditions in the same patient. Absence of uremic symptoms and retinitis, with normal functional tests, should, in my opinion, strongly favor hyperpiesia.

The following case illustrates hyperpiesia in a woman with the history of nephritis in pregnancy.

Mrs. E. I., fifty-one years of age, seen first in 1914. Hypertension, 245/130. She had had a nephritis with the last pregnancy, fifteen years before. The heart showed a moderate

grade of hypertrophy The retinal vessels were negative. Phthalein 60 per cent. in two hours Blood uric acid 12 mg per 100 c.c. Non protein nitrogen 18 mg per 100 c.c. All these are normal figures

In 1917 Blood pressure 230/130 No change in heart noted, but retinal vessels now show sclerotic changes Phthalein 46 plus 21 equals 67 Blood uric acid 4.14 mg per 100 c.c. Urea nitrogen 14.3 mg per 100 c.c. There had been no accidents of any kind in the meantime and, though so high a blood pressure obtained over all this period, the only changes noted were sclerosis of the retinal vessels and a beginning retention of uric acid

The case is not so clear in the following

Mrs D B, forty years of age. Blood pressure 200/120 Had a nephritis with first child, some fifteen years before A second pregnancy was interrupted because of nephritis Very recently she had had a cerebral accident while straining at stool, characterized by numbness in the left hand and elbow, and some difficulty in selecting her words in conversation Her heart was hypertrophied, there was a systolic murmur at the apex and one over the second right space. The retinal vessels showed sclerotic changes Urine, 1017, trace of albumin and a few hyaline casts The phthalein output was 33 plus 18 equals 51 per cent Blood uric acid, 5.4 mg per 100 c.c. Urea nitrogen, 25 mg Creatinin, 1.19 mg Two months later her uric acid was 9.7 mg, urea-nitrogen 29.3 She was put on a rigid dietetic régime and one month later her uric acid was 1.82 mg and urea nitrogen 24.5.

The retention in this case seems greater than could be accounted for by the condition of the circulation, that is, passive congestion of the kidneys, and it may well be that we are dealing with a hyperpiesia in a patient with kidneys already damaged by a previous nephritis

The following case will show how cautious one must be in making a diagnosis of Bright's disease, even when tests have demonstrated functional distress and certain symptoms point to a hasty diagnosis of uremia

The patient was seventy two years old a small, excessively

florid man, who never had put any limitations on the pleasures of life. He was a hearty eater and indulged freely in alcoholic beverages, rather as a gastronome than as a confirmed alcoholic, a gourmet, and a gormand. He was an out-of-doors man, and when he consulted me was on his way South to spend the winter on his yacht.

His blood-pressure was 200/80. The heart showed a tremendous hypertrophy, the left border was 18 cm from mid-sternum. There was a systolic murmur over the second right space, atheromatous aorta. The eye-grounds showed some white patches of exudate, arteriosclerotic retinitis.

Three months before he had been found in a coma and was seen by an eminent specialist, who made a diagnosis of uremic coma. But he promptly came out of this coma, got up and about, and manifested no further symptoms of uremia.

His urine, when he consulted me, was 1017, showed a massive precipitate of albumin and many hyaline and granular casts. The phthalein output was 5 per cent in two hours. The blood uric acid was 2.05 mg per 100 cc (normal), the urea-nitrogen 42.5 mg per 100 cc, the non-protein nitrogen 78.2 (over 100 per cent increase), and the creatinin 4.8 mg (a very marked increase).

I considered his kidneys perilously compromised, and urged rest and the usual régime. He utterly scorned my advice, went on his trip, and fourteen months later reported himself as in good shape, never having had "another attack." Two and a half years later I gathered this history. He went South the winter I saw him and again the next year, 1916, to California in June, 1916, again in the fall, motored across the continent in May, 1917, motored again to Los Angeles in thirty days, returned to Chicago, and from there eastward to New York in four days, and until two weeks ago, June, 1918, nothing had happened to him, and then he had a slight shock. Does this look like Bright's disease?

Here is a typical hyperpiesia with renal decompensation from passive congestion in an arteriosclerotic kidney, having had a cerebral hemorrhage in 1915 called "uremic coma" and three years later another cerebral hemorrhage. He is now seventy-

five years of age and no more obedient to medical advice than formerly

**Renal Findings**—Of 50 cases of hyperpiesia taken for analysis, the findings were as follows

### Urine

<i>Specific gravity</i>	<i>50 cases</i>	<i>Of observed</i>
1010 and under	3 or 6 per cent	6.8 per cent
1011 to 1020	24 " 48 "	54.5 "
1021 to 1030	16 " 32 "	36.3 "
1045 (diabetic)	1 " 2 "	
	6 " 12	not observed

It will be seen that the characteristic low specific gravity of Bright's did not obtain

<i>Albumin</i>		<i>50 cases</i>	<i>Of observed.</i>
In 8 cases	16 per cent.	None.	17 per cent.
In 9	18 "	Very faint trace	20 "
In 19	38 "	Trace	41 "
In 10	20 "	Heavy trace.	22 "
In 4	8	Not observed.	

In about one third practically no albumin by ordinary tests  
In another third a trace In less than one-third a heavy trace.

I am convinced that the trace of albumin is due to the arteriosclerosis in the kidney and the heavy trace to passive congestion in the kidney The first third would have been classified by Mahomed as in the prealbuminuric stage of Bright's disease.

<i>Casts</i>		<i>In 50 cases</i>	<i>Of observed.</i>
These were nearly always hyaline, occasionally granular			
19 cases	38 per cent	None.	42.2 per cent.
19	38 "	Few	42.2 "
7 "	14 "	Many	15.5 "
5 "	10	Not observed.	

### *Phikalein test (Phenolsulphonephthalein)*

	<i>Observed.</i>	
5 cases	10 per cent. (13.9) in two hours	70-80 per cent.
11	22 " (30.6) " "	60-70 "
8	16 " (22.2) " "	50-60 "
6 "	12 " (17.5) " "	40-50 "
5	10 " (16.6) " "	30-40 "
1 case	2 " (3.0) " "	5 "

Thus, two-thirds were normal In none of the cases did I find the low figures so ominous in uremia, except in one whose history I have just detailed In 14, or 28 per cent, the observation was not made

Of the 32 cases noted, 26, or 81 per cent, passed the most of the dye in the first hour, 2, or 6.4 per cent, the same in each hour, and 4, or 12.8 per cent, most in the second hour

**Blood Determination — Uric Acid** — This was observed in 43 cases

Of the observed

24 cases, or 56	per cent.,	showed 3	mg or less per 100 c.c. blood
7	"	16	" " 3-4 mg per 100 c.c. blood
4	"	9.3	" " 4-5 " " "
5	"	12	" " 5-6 " " "
1 case		2.3	" " 6-7 " " "
1	"	2.3	" " 7-8 " " "
1	"	2.3	" " 9-10 " " "

44 per cent. noted showed some retention

56 per cent. noted were normal.

According to Myer and Fine uric acid is the metabolite earliest retained I found this by no means constant, but I did find that it was more commonly retained than the others

**Urea-nitrogen** was observed in 42 cases

Of the observed

20 cases, or 47.6	per cent.,	showed 20	mg or less in 100 c.c. blood
13	"	30	" " 20-25 " " "
5	"	12	" " 25-30 " " "
1 case		2.4	" " 30-35 " " "
1	"	2.4	" " 35-40 " " "
1	"	2.4	" " 40-45 " " "
1	"	2.4	" " 45-50 " " "

Normal is taken at 20 mg or less, 20-25 mg as debatable

We thus have in these two groups 77.6 per cent normal and 21.6 per cent of frank retention Note that only 4 run above 30 and that 48 mg was the most

Non-protein nitrogen in the blood was determined in 12 cases

Of those observed

3 cases, or 25	per cent., showed 35	mg or less in 100 c.c. blood
6 " 50	" " 35-45	" "
2 " 16.66	" " 45-50	" "
1 case 8.33	" " 78	" "

Considerable retention occurred in 25 per cent., of which the highest was in the old gentleman just cited, 35 mg or under was taken as normal

Creatinin in blood was determined in 16 cases

Of those observed

11 cases, or 68.7	per cent., showed 3	mg or under
4 " 25	" " 3-4	" "
1 case 6	" " 4-8	" "

3 mg or under is taken as normal

In this series Dr Mosenthal's concentration test was done in 4 only, as most of these cases antedated the method. Nocturia occurred in all. Slight limitations in concentration in 2. Polyuria in 1.

It will be noted that striking retentions occurred in very few, if any.

My cases of hyperpiesia now number over 250, which, unfortunately, I have not had time to collate, but the results, I am sure, are very much the same throughout. In all the 250 cases or more I have not seen any case die of what I believe was uremia, though it is possible that one did. The clinical picture of all this larger number was not that of Bright's disease. The renal decompensations have rarely been of marked degree, and when treatment was directed toward improvement in circulation and functional rest the improvement has been beyond anything I have ever witnessed in Bright's disease.

I cite a recent case not included in the series of 50. This man of fifty years had a blood pressure of over 300/190. He had a hemiplegia. He was a physical type of the hyperpietic, overweighted, stocky, and florid. The heart was enormously hypertrophied and a systolic blow had developed at the apex.

The renal functional tests showed phthalein output of 15 in two hours, uric acid in blood 6 mg per 100 c c, urea-nitrogen 49 mg, creatinin 7 mg Wassermann negative In four weeks under restricted diet and digitalis his blood-pressure was 240/130, uric acid, 1.57 mg, urea-nitrogen, 20 mg, creatinin, 3.04 mg

I hope I have impressed upon you that this group of cases so commonly called Bright's disease are not such, that the renal decompensation is slight, the phthalein depressed to a greater degree than the metabolites are retained, as one would expect with passive congestion, that improved circulation restores renal compensation to an astonishing degree even in kidneys that have undergone much shrinking from arteriosclerotic changes, and that uremia must be a rare phenomenon in this group

How, then, do they die?

- 1 By an arterial accident
- 2 By cardiac failure

We have seen that when these hypertensive cases are not called Bright's disease they are termed "ARTERIOSCLEROSIS" It has been widely assumed that arteriosclerosis was responsible for the increase of blood-pressure, but now we are coming to believe that it is the result of hypertension rather than the cause, where the association between the two exists

Allbutt has illuminated this subject as he does most with which he deals He divided all arteriosclerosis into two groups

- 1 That form found in elderly people, giving rise to thickened, tortuous, and strikingly calcified arteries, not associated with hypertension to any considerable degree and not associated with cardiac hypertrophy, that form of atherosclerosis commonly called senile, or, as he has termed it, "decreascent" or "involutionary," both of which terms we associate with the waning processes of age

- 2 A form whose pathology is in many respects like the first, but giving rise, as a rule, to thick, leathery arteries, fibrotic, only occasionally calcified (though forms 1 and 2 may coincide), associated with hypertension, whether that of essential or primary hypertension—i.e., his hyperpiesia, or that of Bright's

disease, and, as he convincingly argues, due to the excess of blood-pressure itself. This form of arteriosclerosis is, of course, associated with cardiac hypertrophy.

3 Toxic arteriosclerosis, occurring after infections, notably syphilis, but also typhoid, scarlet fever, rheumatism, influenza, and other diseases more rarely. This is an affection of the middle coats especially, the familiar pathology of lues. It is important to note that this form of arteriosclerosis is not associated with hypertension of any import, and consequently not associated with cardiac hypertrophy. You will again and again find statements of syphilis as the cause of hypertension. These are incorrect, though, of course, lues may occur in a hyperpietic.

Our subject is concerned with the second form only. Now the incidence of arteriosclerosis is more or less haphazard and patchy. It may affect many territories, like the spleen, without giving rise to any disturbance, or it may affect one or more important areas, with death as the result. The kidneys are in a large percentage of cases the seat of arterial changes, in advanced cases causing a starvation and shrinkage of kidney substance with very slow sacrifice of reserve, but rarely, and that on the occasion of circulatory impairment and consequent passive congestion, giving rise to frank decompensation, and we have seen how amenable this state is to proper treatment in contrast to true Bright's. Much more rarely than has been sometimes assumed the splanchnic vessels are seriously involved. We have seen in the case of the young child how a thrombosis of one of the mesenteric vessels caused ulceration, peritonitis, and death.

Two territories are of prime importance, the ~~coronary~~ vessels and the cerebral vessels. I will speak first of the ~~brain~~. Apoplexy is the classical expression of the ~~disease~~ state of the cerebral vessels, and hemiplegia its most ~~marked~~ ~~manifestation~~ manifestation.

F W (male), sixty-six years. Blood-pressure ~~was~~ ~~seen~~ 200/110. Highest noted 240. Hypertension first noted three years before. Slight stroke April, 1915. Second stroke September, 1916. Fatal stroke one year later in '17. Renal



tests practically normal Phthalein 18 plus 24 equals 42 Uric acid 3.22 mg Urea-nitrogen 21.5

C W B (female), forty-eight years Blood-pressure 230/110 First noted one and a half years before Confusion of speech and sudden weakness Six weeks later hemiplegia Phthalein 46 plus 26 equals 72 Uric acid 3.37 mg Urea-nitrogen 14 mg

J C F (male), sixty-three years Blood-pressure 240/130 Slight hemiplegia Phthalein 27 plus 14 equals 41 Uric acid 3.55 mg Urea-nitrogen 21.5 mg Excellent health two years later

All three had arteriosclerotic changes in the retinal vessels. When one considers that these vessels are offshoots of the cerebral vessels, one understands what prognostic significance changes in the retinal vessels affords, for while the patchy incidence of arteriosclerosis permits of changes in the retinal vessels without involvement of cerebral vessels elsewhere, nevertheless these changes make it highly probable that branches of cerebral vessels elsewhere are implicated. You do not have to be skilled ophthalmologists to make useful observations in this field, and I, for one, contend that the general practitioner should carry his stethoscope in one pocket and an ophthalmoscope in another, and use both on every case examined.

The criteria of changes that I have adopted are

- 1 Changes at arteriovenous crossings Displacement (crooking) of veins at arterial crossings

Obstruction or obliteration of veins at arterial crossings

These are most important

- 2 Tortuosity of arteries, especially the small branches

- 3 Central light reflex—the bright glistening streak along the center of the arterial wall This should be considered only in smaller branches and has especial value if the light streak is interrupted in dots

- 4 Irregularity in the lumen of the arteries

- 5 Retinal hemorrhages

- 6 Arteriosclerotic retinitis

Of course, this list is not exhaustive, but will answer the purpose of the general practitioner

Arteriosclerotic retinitis is among the newer concepts and most important to grasp. It consists of the changes constituting the picture of arteriosclerosis plus exudates which are usually seen as small dots, spots, or areas. Not infrequently they occur in groups between the macula and disk. They often occur in one eye only. A retinitis in the presence of hypertension is fairly sure to be diagnosed an albuminuric retinitis by the general practitioner. B. Foster Moore, to whom I am indebted for these remarks and whose article on this subject in the *Quarterly Medical Journal*, Vol. 10, Nos. 37 and 38, I earnestly recommend to you, differentiates the two in these terms:

In sclerosis the changes in the vessels are commonly more marked in proportion to the exudates than in renal retinitis. "Retinal hemorrhages tend to be smaller and more scattered than in renal retinitis. The retinal exudates are to some extent distinctive in appearance and arrangement. Patches of soft edged exudates (wooly patches, cotton wool patches, snow bank, or cumulus cloud exudate) are rare in arteriosclerotic retinitis, and when they occur are probably evidence of beginning renal insufficiency. General retinal edema does not occur. The star figure may be present in either case."

A large percentage of arteriosclerotic retinitis remains unilateral. This is seldom the case in renal retinitis.

Of the 50 cases analyzed, the condition of the retina was noted in 36.

Arteriosclerosis was found in 21, or 58 per cent. Hemorrhage occurred in 6, or 16.6 per cent., exudates in 2 cases, 4 more cases showed signs of arteriosclerosis of indefinite character. If these were included, one would say that two-thirds of the cases of hyperpiesia showed arteriosclerosis of the retinal vessels.

Other expressions of cerebral accidents of minor character are slight, such as passing disturbances of speech, often not amounting to aphasia, but a confusion or difficulty in choice of words, e. g., one of my patients whose pressure varies between 155 and 200 had at table an attack of confusion and bewilderment, accompanied by loss of memory of names of servants who had been in the family over twenty years, that rendered her almost

hysterical This passed off in a few minutes and has not recurred in three years

Mental lag may be an early manifestation, loss of wonted initiative, snap, and go, or it may be unaccustomed irritability and nervousness, carelessly called "neurasthenia" Among the older patients frank mental deterioration is more obvious Convulsive seizures, epileptiform in character, may occur I have had 4 cases in the arteriosclerosis of elderly people Three out of four have been in the senile type of arteriosclerosis, associated with low blood-pressure This seems to be the rule, according to Allbutt Stengel has discussed this group The one case with hypertension was in a man aged sixty-four years who had three attacks in his sleep in the course of five months His blood-pressure was 200/100, arteriosclerosis of the retinal vessels Urine 1015, no albumin, no casts, phthalein 34 plus 23 equals 57, blood uric acid 4.9 mg, urea-nitrogen 17 mg per 100 c.c It will be seen that the kidney was not involved These attacks might carelessly be attributed to uremia

Two of these 50 cases died from an arterial accident If death is not due to this cause it is usually a cardiac death

**Cardiac Disease in Hyperpiesia**—So prominent are the cardiac difficulties in many cases of hyperpiesia that the presence of hypertension or its rôle in the drama is overlooked, and the condition diagnosed as cardiac disease, as myocarditis, angina pectoris, etc

Two conditions contribute to cardiac changes in hyperpiesia, especially (1) increased work entailed by increased pressure, and (2) changes in the coronary vessels of a sclerotic character affecting the nutrition of the myocardium

Cardiac hypertrophy is constant in hypertension, as might be anticipated This hypertrophy is unquestionably compensatory, but that the quality of such a musculature is as good as the normal is more than doubtful A veritable *cors bovinum* does not mean an increase in efficiency in proportion to increase in weight Impairment of the coronary circulation must mean malnutrition, degeneration, increase in connective-tissue ratios, disturbances in rhythms, and probably far more subtle changes of a physico-

chemical nature that waits upon the future for elucidation, but which is demanded in many cases of so-called myocarditis and senile heart, whose failure of function unto death displays such a paucity of pathologic change in structure at the autopsy table. I am in accord with Christian's observations and teachings on this subject.

**Pulmonary Edema.**—This is a not uncommon accident in hyperpiesia, indeed, it is a phenomenon peculiarly associated with left-sided heart failure. It would take us too far afield to discuss its causation in detail. Perhaps the most appealing explanation is an accumulation in the pulmonary circuit, due to disproportion in the two sides of the heart, an efficient right heart forcing blood into the pulmonary arteries, an inefficient left heart emptying the pulmonary veins. However, this fails to explain to me the sudden onset, the rapid clearing up, and its occurrence without physical exertion or mental agitation to account for it, as is the case in many instances. Of course this may be the cause of death. On the other hand, it is surprising how many attacks of this kind, each of which seems alarming, the patient may survive. Here is one in this series of 50 cases, a man of fifty-seven years, blood pressure 200/110, with normal blood constituents, who has had several attacks of pulmonary edema. The tic-tac quality of his heart sounds pronounced his needs, and with the aid of digitalis he passed the next year with only one slight attack. Several of my patients have had these attacks.

Angina pectoris is fairly common among the cases of hyperpiesia. Accepting any of the common explanations of the phenomenon, one would expect angina to be frequent in these laboring hearts, the seat of probable coronary sclerosis and associated with atheromatous aortas. And yet, in my experience, the angina in these hypertensive cases has been more benign in its course than in the low blood-pressure cases of senile arteriosclerosis. Indeed, I have come to dread the cases whose pains and distribution of pains are classical, but whose hearts seem normal in all respects to an examination and whose blood pressure is normal.

Six of my series, 12 per cent., had angina with as yet, so far

as I have been able to trace them, one death only. The fatal case when I saw him was sixty years old. Blood-pressure 178/80, blood constituents normal, heart grossly incompetent. Death occurred three weeks later.

Among the non-fatal cases is a physician of sixty-five years. Blood-pressure 195/100. Practically normal renal tests. Enormous hypertrophy with evidences of conduction defects. Suffering from frequent and crippling attacks, obliging him to give up his practice, and yet after many months resisting their fatal effects.

Another of forty-five years, having gout and, except for blood uric acid, which at the time of a gout attack rose to 9.1 mg, showing normal renal tests. Blood-pressure 225/140, unable to walk a block without some anginal pains, but, observing these limitations, remains relatively comfortable. Wassermann reaction negative.

Here another, a woman of fifty-two years. Blood-pressure 265/145. Renal tests normal. She is pitifully affected, pains severe, and occurring continuously even at complete rest, necessitating so much drug relief that at last it is hard to estimate the degree of suffering as against drug craving, and this has gone on month after month, with no threat of an attack of fatal severity or sign of cardiac failure.

All of the cases cited evidenced involvement of the root of the aorta, hence possible involvement of the coronaries, the usual explanation of angina, and fortifying Allbutt's idea of implication of sensory nerve plexuses at the root of the aorta as the cause.

**Paroxysmal Dyspnea** —Somewhat akin to angina pectoris is another reflex nerve storm, paroxysmal dyspnea. I have 2 cases in my series. It consists of a most intense and abrupt dyspnea of agonizing character, equalled by nothing that I have witnessed unless it was a similar attack I once saw precipitated by an injection of diphtheria antitoxin (horse-serum) in an asthmatic sensitized to horse emanations, which well-nigh proved fatal. Like this anaphylactic reaction, paroxysmal dyspnea is caused through a violent contraction of the bronchioles and is attributed by

Longcope,<sup>1</sup> whose most excellent study of this condition I recommend to you, to an involvement of these same nerve plexuses at the root of the aorta in an aortitis

This patient, fifty three years old, had had these attacks for six months, latterly many in a day. Blood pressure 220/150. Angina accompanied them. He died not long after.

The second case was in a woman of seventy years. Blood-pressure 280. I did not witness these attacks.

Cardiac irregularities are of frequent occurrence. The most common are the premature systoles, the importance of which has diminished in my estimation almost to the vanishing point. I have one case (not a hypertension) in whom a strip of an electrocardiogram showed premature systoles to frankly outnumber the normal complexes, with no evidence of impairment to the circulation, subjectively or objectively.

Paroxysmal tachycardia has been fairly frequent in my series, and, moreover, except for the annoyance of the attacks, the patients have been none the worse for it. A paroxysmal tachycardia, you will recall, is really a series of auricular premature systoles, and an auricular premature systole is a beat initiated from some point or muscle-fiber in the auricle other than the pace maker, the sino-auricular node of Keith Flack. It is an ectopic beat, an abrupt shifting of the pace-maker from its normal site to an abnormal one, hence, the transition must occur between beats, and the onset and offset—*i. e.*, cessation—must be abrupt between beats, in contradistinction to the gradual waxing and waning of physiologic tachycardia. The rate varies usually between 140-200.

I have 4 cases in this series—*i. e.*, 8 per cent.

A man, fifty-six years old, blood pressure 230/120, normal renal findings, extensive pulmonary tuberculosis, had the attacks for years. I was able to teach him how to stop the attacks by pressure on his right vagus nerve as it coursed in the carotid sheath.

A second case had had his attacks since boyhood. When I first saw him he was fifty two years old, a well-developed man of

<sup>1</sup> Archives of Internal Medicine, vol. II, No. 1

florid complexion who looked the picture of health. His blood-pressure was 180/100, his renal tests normal except that his blood uric acid was 5.3 mg. The heart was hypertrophied, showed premature systoles that the electrocardiogram demonstrated arising from the right base. He had long ago learned how to control them by a maneuver: he would sit down, draw himself together, then get up, stretch his arms widely, and the attack would stop. Patients learn one maneuver or another that stops the attack, all of which are analyzable into stimulation of the vagus, mechanical or physiologic.

Another case was a woman fifty-seven years of age. She has been under my observation for seven years. When I first saw her the blood-pressure was 230/120. It has rarely if ever been below this, often more. She is very athletic and exercises hard with impunity. She has a huge hypertrophy, a systolic murmur over the second right space, and premature systoles. She has had tachycardia for years, but singularly enough, and for what reason I do not know, the attacks have ceased in the last two years.

**Auricular Fibrillation** —Janeway has said that auricular fibrillation is rare in this class of cases. I have one case, proved by an electrocardiogram, a man of fifty years of age, who when I saw him was fairly waterlogged as the result of a gross decompensation. At this time his blood-pressure was 130/80, but his physician had read his blood-pressure at 162/80, and he had an enormous hypertrophy of the left ventricle which bespoke a long-standing hypertension.

Janeway's statement I believe to be correct and, indeed, we know that the vast majority of cases of auricular fibrillation are furnished by mitral stenosis and the senile heart, under neither of which categories do the hypertrophied hearts of hypertension fall. It has frequently been noted that hypertension occurs not uncommonly among cases of *mitral stenosis*. Statements to show that these cases are associated with fibrotic kidneys and arguments to demonstrate that the nature of this association is (1) accidental, (2) due to a same cause, (3) the fibrosed kidney is due to the mitral lesion, and (4) the

mitral lesion is due to the fibrotic kidney, have been well presented by Cowan and Fleming in the Quarterly Journal of Medicine, 1912 I have seen this association several times

One case, in a woman thirty nine years of age, I had under observation for ten years, saw the mitral stenosis develop, and some years after its incipency, saw the hypertension follow A soft apical systolic murmur was heard in 1907, a distinct murmur in 1908, a presystolic in 1911 At this time her hypertension was first noted Her blood pressure in 1911 was 160, later in the year 180, in 1912, 210/115, after that it ranged about 200/120 In 1914 she was pronounced by one of the ablest diagnosticians of the day a case of chronic interstitial nephritis Urine 1024, trace to heavy trace of albumin, few casts seen in 1915 Phthalein test 26 plus 25 equals 51 Blood uric acid 1.7 mg per 100 c.c. Non protein nitrogen 23 mg per 100 c.c., later, McLane index, determined at the Rockefeller Institute in this city, 91 to 112 She is still living and has shown no symptoms of uremia in all these years

Here is another case Woman, forty nine years of age Blood pressure 210/100 to 230/130 Noted first four years before. Heart, mitral stenosis Had several attacks of edema of the lungs, first four years ago Urine 1014, faint trace of albumin, few hyaline and granular casts Phthalein 32 plus 22 equals 54 Blood uric acid 2.2 mg per 100 c.c. Blood urea nitrogen 15.75 mg per 100 c.c.

Here is still another with the history of a rheumatic endocarditis and with a mitral insufficiency with a blood-pressure of 185/120, but mitral insufficiency is so common in hyperpiesia due to relative insufficiency that one must accept the diagnosis of rheumatic endocarditis with reserve. Murmurs are common enough. Systolic murmurs at the apex alone occurred in 22 per cent, at base in 28 per cent, and at base and apex in 14 per cent.

Systolic and diastolic at base 2 per cent. Presystolic at apex 4 per cent Murmurs of aortic origin in 44 per cent.

Murmurs at the base, in second right space, I look upon as evidence of an atheromatous aorta



Murmurs at the apex, unless presystolic or accompanying a presystolic, as due to relative insufficiency, though one cannot exclude in a small percentage sclerotic changes in the mitral valves

**Excessive Pressures**—It is always a source of surprise to note how long and how well excessive pressure may be borne. Indeed, the more I see of hyperpiesia, the less importance I place on the reading alone. High diastolics disquiet me decidedly more than high systolics. It takes a good heart to pitch a high systolic, but a high diastolic strains an already diseased artery. I fancy that among my patients those with a large pulse pressure have done very well. It means heart force, no great arterial strain, and an efficient wave sent to the periphery.

For years I have watched one patient already cited in discussing paroxysmal tachycardia with a blood-pressure from  $\frac{230-260}{120}$  and very active in all her exercise all this time. Another, a woman of fifty-three or fifty-four, I watched some half a dozen years before she developed anginal pains, her blood pressure was rarely below  $\frac{240-270}{100}$ . She must have borne this pressure some years before I first observed her. Still another, a woman of sixty, blood-pressure over 300 in systole (my sphygmomanometer measured only 300) and 120 diastole. How long she had had these high pressures I do not know. Under treatment one year (fourteen months) her pressure taken then showed  $\frac{270}{180}$ , two months later,  $\frac{250}{90}$ . I lost sight of her some months later, though she was still doing well. It will be noted that all had a large pulse pressure.

**Early Cases**—Allbutt says "If we can catch hyperpiesia early and keep at work against it, it can be cured more often than not." He then adds "When the system has taken a new set, the whole has readjusted itself to the altered conditions and the new attitude is more or less permanent." This statement is an important one, for it means that when the cardiovascular system has undergone certain structural changes, a hypertension becomes a physiologic necessity and efforts to reduce a blood-

pressure to normal are abortive or, worse yet, attended by serious injury to the organism

To the pertinent question, How is one to know whether the condition is an early one or no? he replied by suggesting that the criterion be the response to rest and simple treatment. In the early cases the cardiac outline recedes to normal proportions and the pressure falls to normal

The essentials of treatment are rest, physical and mental, and a regulation of diet. Our great limitation comes in the fact that these cases are "caught," as he expresses it, only accidentally, in the course of a routine examination, a life insurance examination, or examination for other causes in a presumably healthy subject, for the early cases give rise to no symptoms that lead the subject to seek medical advice

A pressure of 140 or more in systole in a young or middle-aged man or woman, if it is persistent, and even more, a diastolic of 100 or more should be looked upon with grave suspicion, carefully investigated, and the kidney having proved innocent, be considered as an early hyperpiesia.

Here is a man of forty five years who presents a blood pressure of 140/100, his heart shows slight hypertrophy, his palpable arteries are thickened, the vessels of his retinae hint at change, his urine is of a specific gravity of 1027, no albumin, and no casts. His blood uric acid is 1.4 mg, and his urea nitrogen 21 mg per 100 c.c. This is certainly an early case.

My best results have been in the obese with hypertension, in whom a modification of diet was awarded with results

Unfortunately, many early cases feeling as well as they do will not submit to the period of rest demanded or rebel at dietetic restrictions, so that we see the case develop under our eyes as I have in two of the cases of this series

Treatment.—This talk is given with the especial object of making you recognize this group as an entity, but a therapist may hardly be pardoned if he close a dissertation of this sort without mention of the treatment. Indeed, as a therapist and feeling that the end and aim of the study of medicine is the cure of disease or amelioration of the distresses of disease, most articles

on medical subjects seem to me Hamlets with Hamlet left out, because treatment receives so scant courtesy in them

*Rest in Bed*—I have mentioned the excellent results of rest in bed in cases of early hyperpiesia. I am inclined in any case to study the effects of rest in bed for a week or two and further to study the after-effects. In most cases a fall of pressure occurs to some extent, but in those cases which have "taken a new set," as Allbutt puts it, the blood-pressure goes up again when the patient is once more up and about. This variation, indeed, might be anticipated as expressive of changes in physiologic demands.

Rest in bed has a special value in those cases in whom a sudden access of hypertension, so-called hypertensive crises, have occurred, and, finally, rest in bed is imperative when premonitions of cerebral accidents are noted and when any degree of cardiac decompensation is determined. The length of time depends on amelioration of symptoms, but it must be remembered that too prolonged confinement of weeks' duration is prejudicial, especially to the aged.

*Diet*—Many, frankly, the majority of these patients are hearty eaters, the florid, beef-eating, English Squire type. Some are obese. Many, however, are neither florid, obese, nor hearty eaters. Allbutt thinks diet plays a considerable rôle in the causation of the condition. Work by Gettler shows that the plasma solids and the refraction indices of the plasma are much increased in this class of patients in contrast to the hypertensive cases of Bright's. Unpublished observations made in my wards would seem to corroborate these findings (laboratory work done by Dr Gettler and assistants). One might conjecture some association between these changes and those in viscosity.

It has been my custom to make most of these patients practically vegetarians, limiting them to 48 to 56 grams of protein a day, this is easily accomplished on a vegetarian diet. Of late I have felt that complete exclusion of meat was not wise in all cases, but have tried to restrict the protein to the same extent, but allow a more varied and palatable selection.

The total intake is to be considered. The best results I have had have been in the obese who underwent a reducing diet. In

this class the close relation between the quantity of food ingested and pressure seems convincing. Here starches and sugars undoubtedly play a rôle.

When Dr. Robert Cooke was studying some phases of hypertension on my wards at Bellevue we were convinced that in some cases at least the ingestion of salt increased the blood pressure. It is my custom to limit the salt intake to that quantity necessary in cooking to make the food palatable, asking that it be discarded as a condiment and urging the use of unsalted butter. All condiments and rich sauces and gravies are excluded.

As regards the quantity of fluids to be taken, I have advised that the patient's thirst dictate this, feeling that when salt, condiments, alcohol, and rich sugary foods are excluded the demand will not be excessive. Of course, in the presence of cardiac decompensation a marked restriction in fluids is often most beneficial. Alcoholic drinks, I think, should be interdicted, though the habits of a lifetime may in individual cases make a compromise desirable not only for the comfort but the welfare of the patient.

*Bowels*—I am in no way convinced that the condition of the bowels has anything to do with hypertension, but abnormal fermentations and putrefactions undoubtedly add, through absorption of their products, burdens to the organism. For that reason I am accustomed to advise blue mass, 3 to 5 grains, once a week and some saline in not too drastic doses once a week between the mercurials, and in the chronically constipated, in addition, milder cathartics or measures such as are usually effectual in such cases.

*Habits and Exercise*—A man with hypertension should be warned to make his life less strenuous, to beware taking on new enterprises that entail great mental stress, to make his holidays more frequent and a little longer, to make his business hours a little shorter, but by no means make an invalid of him. Divorcing these people from their work and their life's interest often works great harm. They go to pieces frequently with astonishing rapidity. Even when the heart begins to manifest shortcomings or minor cerebral accidents have occurred, when once the one

has been remedied as far as possible and the other has had time to repair, a return to their interests is beneficial

For patients with hyperpiesia exercise is important. When heart and vessels seem competent I have not limited the amount or character of exercise unless it entails places in which an apoplexy might jeopardize life, as in swimming. One of my patients, a woman in the middle fifties, walks several miles each day, skates enthusiastically in winter, and plays tennis, often several sets a day, in summer. Though I have watched her for a number of years I have seen only good come from it. Most patients of the hyperpietic age choose less vigorous forms of exercise, such as walking, the best of all, and golfing. In those with cardiac limitations exercise must be adapted to the state of their circulation and the same methods followed as in other cardiac cases. Sudden exposure to cold should be avoided and clothing chosen to avoid sudden chilling of the skin. High altitude should be approached gradually, and much above 1500 feet entails a risk to heart and arteries.

**Treatment of the Hyperpiesis**—Again permit me to emphasize the necessity of studying the patient with reference to his reaction to his hyperpiesis. That pressure at which he feels best and at which his functions are best subserved is his *optimum* pressure, regardless of figures, and is not with impunity interfered with. Do not interfere by the use of *dilators* unless heart or artery gives the signal. If you succeed in lowering the pressure your patient may be much worse off than before, commonly you do not succeed. When the blood-pressure has rapidly shot above its accustomed figures, a sense of unwonted fulness or headache warns of impending danger, or the heart is obviously laboring without results against a burdensome pressure, then use the dilators.

The nitrites are the choice, nitroglycerin or erythrol-tetranitrate. The former may be given in such doses as accomplish the object or provoke the unbearable headache that compels you to stop. I do not know what the toxic dose is. Give  $\frac{1}{100}$ ,  $\frac{1}{50}$ ,  $\frac{1}{25}$ , or  $\frac{1}{10}$  grain every two hours if needed. If headache occurs before any fall is observed, do not use it again, try chloral, 5

grains, at four hour intervals or four doses a day. This should be used only a few days at a time, cautiously, when the heart is weak, and stopped when drowsiness by day is marked. In those troubled with much insomnia no doubt the sleep it affords works favorably on the hyperpiesis. The iodids have a traditional usage, but I am inclined to question their efficiency. They are prone to upset the stomach. They are said to give good results in syphilitic cases, but lues does not cause hypertension.

High frequency current is highly lauded by its advocates, even Allbutt speaks a very good word for it. He says its failure is due to too limited usage. (He quotes from Humphris.) The technic of this proceeding must be sought in articles especially devoted to the subject. I have submitted several patients to efficient hands, but have been very poorly impressed with the results. However, I have had astonishing results cited me by good observers.

Venesection has impressed me more favorably. I have taken 10 to 16 ounces of blood from patients with satisfactory results. I have not observed a sudden fall after the withdrawal, rarely more than 10 mm, sometimes none, but many patients feel better, get a relief of the sense of fulness in the head, and seek voluntarily for further bleeding. The results are sometimes astonishingly lasting, even for several months.

I might lengthen this already much too lengthy discourse by discussing the treatment of the various conditions to which hyperpiesia leads—apoplexy, cardiac decompensation, angina pectoris, tachycardia, etc. But these must be deferred to other times and places. I hope I have convinced you that there is a distinct entity characterized by hypertension, hyperpiesis, as Allbutt prefers to call it, and to which he has given the name hyperpiesia, often mistaken for Bright's disease by physicians and pathologists, but which claims no kinship to Bright's in its symptomatology or its ultimate issue.



## CONTRIBUTION BY DR WILLIAM H PARK

LABORATORIES OF THE NEW YORK CITY DEPARTMENT OF  
HEALTH

### PRACTICAL IMMUNIZATION AGAINST DIPHTHERIA<sup>1</sup>

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Discovery and Development of Artificial Immunization against Diphtheria. Experimentation, Animal and Human, and Results  
Extent of Natural Immunity Valuable Aid in Schick Test  
Description of this Reaction and its Uses, Experimental and Practical, Confusion Caused by Association of Protein Sensitization and Method of Differentiation Necessity of Accuracy and Standardization. Assurance of Practical Immunity against Diphtheria in Man. Absolute Harmlessness of Injections  
Time of Development of Immunity Duration of Immunity  
The Toxin-antitoxin and Its Practical Application. Selection of Cases for Immunization Results in Five Representative Institutions

THE first idea of the immunizing power of the diphtheria toxin modified by the antitoxin came accidentally through the fact that a number of the guinea pigs used to test the potency of diphtheria antitoxin survived This potency test is carried out by mixing certain quantities of the horse-serum of unknown antitoxic strength with a number of fatal doses of diphtheria toxin In carrying out the test a certain proportion of the animals usually receive a mixture which overneutralizes and, therefore, is not poisonous. Some of these guinea-pigs kept for a number of months were again used for antitoxin potency tests, and it was found that although they had not been poisoned by the toxin-antitoxin mixture, they nevertheless had developed im

<sup>1</sup> Lecture addressed to the monthly class of Military Surgeons at the New York University and Bellevue Hospital Medical College, May 13 1918



munity through the stimulus of the toxin in the slightly over-naturalized mixture

The first use made of this knowledge was in the rapid immunization of horses. It was found that by giving a mixture of toxin and antitoxin the first injection of toxin could be very much larger than if the pure toxin were given. It was also found that if haste were required in producing potent antitoxin, large amounts of this apparently neutral mixture could safely be given at short intervals, and the horses would produce potent serum within a few weeks. Thus, in 1905, I reported that horses had produced as high as 400 units per cubic centimeter after six injections of this antitoxin mixture.

Soon after these successful experiments the possibility of immunizing human beings susceptible to diphtheria occurred independently to several laboratory men. The first to suggest it in writing was Theobald Smith. A number of difficulties, however, made this at the time impracticable. The fact that animals received these injections without any poisonous effects seemed to guarantee that human beings would also find the mixture harmless. There was a certain hesitancy, however, in accepting the animal experiments as full proof that these injections would not be deleterious to man. The most serious objection was the fact that we knew from careful testing of human blood in guinea-pigs that some 50 per cent. of children and some 80 per cent. of adults were already immune to diphtheria. This knowledge regarding any person could only be obtained by actually taking blood from the individuals to be immunized, and the only way that successful results from the injections could be estimated would be to take and test additional bleedings from time to time. The time and annoyance consumed in these investigations of each individual case almost prevented any thought of a general use of the immunizing mixture. It had been found meanwhile that in animals which possessed no natural antitoxin, toxin injections were followed by a very slow immunizing response. For instance, 12 guinea-pigs were given by me a full size injection. At the end of four weeks only 2 had become immune, at the end of eight weeks 8 had become immune, and at the end of twelve weeks the

11 surviving had all become immune, the twelfth guinea-pig having died of an accidental infection due to other causes. The response was entirely different in those having natural antitoxin.

In a series of 10 horses, 9 of which had traces of antitoxin in their blood, a marked immunizing response developed within twelve days, from 0.1 to 1 unit per cubic centimeter of antitoxin present before the injection, there developed from 3 to 5 units per cubic centimeter in different animals, while in one horse that had no antitoxin no appreciable response took place before four weeks. It was, therefore, fair to assume that in human beings the same results would take place, that is, those who were immune through antitoxin would develop very quickly additional antitoxin, while those possessing no antitoxin would have a delayed but nevertheless final antitoxin production.

A test was developed meanwhile which enabled us with the greatest ease to determine whether antitoxin was present or absent in any individual. This is now familiar to all as the Schick test. The development of this was interesting. In order to save guinea pigs it had become the custom to inject intracutaneously small amounts of the toxin-antitoxin mixture which had been made to test the potency of the different lots of serum. It had been found that a roughly accurate estimate could be made by observing whether the injection was followed by inflammatory reaction in the skin or not. The degree of the reaction also gave an indication as to the excess of the toxin in the mixture. It occurred to Schick that if a definite quantity of toxin were injected intracutaneously in individuals to be tested, this small amount of toxin would, in the absence of any antitoxin in the skin fluid, cause a little inflammatory reaction shown by hyperemia and slight swelling. After a number of tests he found that 0.02 of a minimum fatal dose for a 250-gram guinea pig was an amount which, in the absence of antitoxin, would cause in from twenty-four to forty-eight hours a marked hyperemia of the skin, with an area the size of a 25-cent piece. This was accompanied with some infiltration and later slight desquamation. A brown pigmentation usually remained from a week to over a month. He

found that if sufficient antitoxin was present in the body to insure immunity there would be no response to the toxin, as it would be neutralized by the antitoxin in the skin fluid. Faint traces of antitoxin would lessen the intensity of the Schick reaction. If desired, a rough estimate of the amount of antitoxin could be determined by giving slightly larger amounts of toxin. This, however, was only used for experimental purposes.

Schick soon noticed that in the older children and adults a considerable percentage showed a protein reaction which had nothing to do with the toxin. In these cases, even when the mixture was overneutralized with antitoxin, this same pseudoreaction developed. In most cases this reaction came on more promptly, covered a larger surface, was more of the urticarial type, and disappeared within three days. In a small percentage, however, it was very difficult to decide between a true and a pseudoreaction, and especially when a true reaction was combined with a pseudoreaction to decide how much was due to the toxin and how much to the non-toxic protein, because the fact of the development of a true reaction in no way prevented the protein reaction.

The best practice, therefore, in adults is to inject the toxin in the skin of one arm and the heated or neutralized toxin in the other arm. In this way the amount of protein reaction can be noted and it can be decided whether the reaction following the toxin is a simple, true reaction, a pseudoreaction, or a combined reaction. Even after the eye has been thoroughly trained, it is still wise to use the two injections when possible. On other occasions only one injection is made, and any cases which remain in doubt are retested or considered as true reactions.

I think it is apparent to all that the Schick reaction, although a very simple test, must be carried out with the greatest accuracy or the results will be entirely misleading. If the toxin has been diluted and stored it may readily deteriorate, and instead of giving 0.02 of a fatal dose, only one-half that amount may be injected and no toxic reaction will occur, and the misleading idea is given that the person has been shown to be immune. If the toxin is carelessly diluted and a large surplus of toxin is given, slight

necrosis may develop at the point of injection. Twice in New York State this accident has occurred and some hundreds of people developed very sore arms. The neutralized or heated toxin used for the pseudoreaction must equally be carefully prepared. If possible the altered toxin used in the control test should be from the same preparation as the toxin used, so that the non toxic protein will be similar in amount and kind, otherwise no comparable response can be depended upon. Recently, at one of the large concentration camps, I believe insufficient care was used in preparing suitable toxin and protein solutions, so that in comparing the two injections they falsely assumed that the difference was always a true Schick reaction, and in this way obtained the remarkable result that some 60 per cent. of the troops were susceptible to diphtheria, and that the individuals that showed positive or negative Schick reactions changed from month to month. These results, which are contrary to those obtained by all other trained observers, would be readily explained by the simple fact that they used injections of materials improperly standardized.

The first attempt to use the injections in man was in 1913, when von Behring actually tested the practical value of over-neutralized toxin injections in children and adults, and after a few weeks' experimentation made a very optimistic report in which he stated that within two weeks over 60 per cent. became immune. A study of his figures revealed the fact that he had not tested the individuals before immunization as to whether they already had antitoxin or not, and this undoubtedly led to his erroneous opinion of early favorable results. Von Behring's first immunizations, although misleading in their results, furnished the world with the evidence that the injections were harmless, and they stimulated a number of us to investigate in a more accurate way the value of the attempt at active immunization. The important facts to be determined were (1) The amount of toxin and number of the injections and then the harmlessness when used at all ages, (2) the response in the way of immunization, and (3) the persistence of the immunization if it occurred.

In New York Dr Zingher and I, and later others of our co-

workers in the Health Department Laboratory, began by testing through the Schick reaction the children in our contagious disease hospitals. Those who gave positive reactions were given the injections. Schick tests were done from time to time, and we followed the responses not only while the children were in the hospitals but also for months after they had returned to their homes. The results showed themselves to be so very favorable that some fifteen institutions, in which large numbers of children were gathered and where they remained for a number of months or years, were also taken into the investigations. For the last three years we have had these institutions under observation. We also were able to test, immunize, and keep under constant observation the infants and children at the Home for Hebrew Infants in which the attending physician, Dr Alfred Hess, and the pathologist, Dr Julius Blum, are both connected with the Department of Health Laboratory. Later, army camps and additional institutions in which infants and older children were cared for were added to those in which the immunizations were first carried out.

Although only three years have elapsed since considerable numbers have been immunized, the results are so favorable that the practical immunization of the child and adult is assured. The response in young infants who are at the time passively immune through transfer of antitoxin from the mothers is still under investigation.

We will now take up in detail a few of the more important phases.

**Harmlessness of the Injections**—Animal experimentation showed that in them an amount of antitoxin sufficient to neutralize the poisonous action of the toxin could be added without interfering with the production of antitoxin. It was found that the best results were obtained with a toxin just sufficiently neutralized to prevent its poisonous effect. With this knowledge, the first immunities in human beings were brought about in adults, and then, as experiments showed that no harmful results developed, children and, finally, infants were immunized. During the past few months careful observations have been carried out in a

number of infants in institutions Many as young as four days have been injected Careful observations are made of temperature changes, weight, appetite, the effect on the blood, and changes, if any, in the urine Except in an occasional infant in whom a slight rise in temperature occurs, no other changes have been noted, even the pseudoreactions which occur in older children and adults are absent in the infants, and in only about 10 per cent. is there even a slight redness at the point of injection It seems, therefore, that these injections can be considered as absolutely harmless It is necessary to emphasize that the toxin broth employed should be carefully prepared so that no other bacterial poisons than those of the diphtheria bacillus be present, and that the neutralization by the antitoxin should be thoroughly controlled by animal tests before it is used in the infant or child

In possibly 20 per cent of older children and adults the pseudoreactions may at times be fairly marked, so that considerable local and some slight constitutional disturbance may be noted These are less severe than in typhoid vaccine inoculations Contrasted with the use of vaccine virus to prevent smallpox the reaction is much less, in the latter we are using a living virus and must expect the development of a local ulceration and of considerable constitutional disturbance, and there is always the possibility of infection None of these conditions can possibly develop with the diphtheria toxin antitoxin injections

**The Time of Development of Immunity**—The observation of a large number of individuals showed that, as in animals, no appreciable immunity takes place in any who have no antitoxin at the time of injection until two weeks have elapsed. This prevents the use of active immunization to stop quickly an outbreak of diphtheria in a camp or an institution At about the fourteenth day a small percentage show sufficient immunity to give a negative Schick reaction Week by week the percentage of immunes increases, until by the eighth week about 80 per cent. are immune, and by the twelfth week 96 per cent. By the end of four months the full percentage has developed, which is about 98 per cent. The remaining 2 per cent. if re-injected have, so far as we have observed, always become immune

It has been found that three injections give a somewhat higher percentage of development of immune persons and a somewhat greater accumulation of antitoxin than two injections, and that two injections give decidedly better protection than one injection. It may readily be that by increasing the amount of the injections a single treatment may give sufficient immunity. At the present time we are trying by increasing the doses to reduce the three injections to two or one. Up to the present, however, the three-injection method is the standard one to be adopted. The larger amounts for the one- or two-injection methods are still in the stage of experimentation.

**The Duration of the Immunity**—We have now had under observation something over 1000 infants and children who were susceptible and became immune through the antitoxin injections. These have been tested at the end of a year and at the end of two years, and some at the end of two and a half years. At the present time only 2 per cent. of those who became immune have apparently relapsed and become susceptible. It seems, therefore, as if a person becoming actively immunized develops a condition similar to those who are naturally immune, that is, the stimulus to produce antitoxin given by the toxin-antitoxin injections has started the cells to produce without reference to any further stimulus of the toxin. This joins these persons to the 80 per cent. of the population who naturally develop antitoxin. At any rate, we are sure that up to two and a half years only 2 per cent. have lost their immunity. Each additional year will give us further proof as to whether this immunity, like natural immunity, is persistent for the duration of life.

While we have been observing the children who have been immunized we have also been following up the greater number which showed a negative Schick reaction. Those who have passed the age of four when tested have continued to show a negative reaction. An interesting series of observations on very young infants revealed the following. Schick tests were made shortly after birth and then at intervals of three months on a series of infants. A number have now reached the age of four years. We found that during the first year of life, of 88 infants

that were negative to the Schick test, 13 changed to a positive reaction, during the second year of life, of 75 negative to Schick, 10 changed to a positive reaction, during the third year of life, of 61 negative to Schick, 3 changed to a positive reaction. Undoubtedly many changed to a positive reaction and then back to a negative one between the tests, the passive immunity giving way to an active one. These changes in early life are due to the fact that the infants inherit passive antitoxic immunity from their mothers. This disappears usually some time after the first six months and within the first two years, but in a few it persists during the third year. When frequent tests are made we have found that the great majority of infants at some time become positive to the Schick test, and then, as they grow older, 80 per cent. of them become immune. This takes place usually during the first four years, but a small number develop immunity up to the tenth year or even later. The fact that a person who has once developed immunity, either through natural causes or through immunization, holds this condition probably throughout life makes a Schick test of extreme value because both the persons who have become immune and those who have charge of them are reassured when in the presence of diphtheria. A woman who has a negative Schick test has the comforting knowledge that her offspring will certainly be immune during the period of infancy.

**The Toxin-antitoxin and Its Practical Application.**—The material injected consists of diphtheria toxin made in the usual way for the injection of horses, except that somewhat greater precautions are taken in the preparation of the meat broth before the inoculation with the diphtheria bacillus. Before use this toxin is ripened by allowing it to stand at a moderate temperature until the first changes in toxicity have ceased. This toxin, which is now quite stable, is then tested for its potency, and is so diluted that 1 c.c. will contain about 200 fatal doses for a guinea pig. This is then slightly overneutralized with antitoxin. The most effective mixture is the one which when given in a very large dose to a guinea pig will cause either no symptoms or very slight paralysis. This has been found to be an absolutely safe mixture.



and one that will produce the greatest amount of immunity in a human being. This preparation is kept in the ordinary vials at a temperature not exceeding 70° F, and is good for at least a year. It can be obtained from the Department of Health of New York City and from the larger manufacturers of bacteriologic products. The injections should be made subcutaneously, the most convenient place being usually the left arm. Any portion of the body, however, gives equally good immunizing results.

At the present time I usually give three injections at weekly intervals. Under certain conditions, where there is no immediate probability of infection, a single injection is given, and at the end of three months a Schick test done. About 60 or 70 per cent. will be found to have been immunized and only the remainder will need an additional two injections. It is, however, often so difficult to be sure of being able to get hold of persons at a later period that the usual three-injection method is the most advisable. As I stated earlier in this lecture, further experimentation may perfect the method so that a single large dose may suffice.

In the thousands of injections carried out there have not been any serious deleterious after-effects. With the early preparation, three children developed some immediate symptoms of protein poisoning, but they all recovered completely within forty-eight hours. These symptoms were probably due to the fact that the broth for the toxin was made in the old way, in which the meat was allowed to ferment in the incubator in the preparation of the broth before inoculation of the diphtheria bacilli. This is a suitable method for preparing toxin for injection into the horse, but is not suitable for use in man.

**Selection of Cases for Immunization**—Vital statistics teach us that the greatest mortality from diphtheria is in the second year of life. The infant at birth, possessing immunity transferred to it by its mother, by the end of six months may have lost this protection, and sickness and death from diphtheria rapidly increase during the second six months. At the end of the second year a number of susceptible children begin to develop natural immunity and, in addition, their great strength enables them to withstand the disease, so that the number of deaths which are

highest in the second year of life gradually lessen from then on. Older children and adults, although they may develop a considerable amount of diphtheria, seldom die from the attacks, especially since antitoxin has been in use.

With these facts before us it is easy to realize that when we consider the population as a whole, the most effective period in which to apply immunity is during the first six months of life. Fortunately, the fact that infants receive the injections with so little disturbance makes this probably the best period of life to receive them. The above observation applies to the population as a whole.

It will undoubtedly be many years, even if our hopes as to the permanent persistence of active immunization are fully realized, before this method of treatment will be in general use. It is important for us, therefore, to consider under what conditions immunization should be carried out. In institutions where children are gathered together immunization is of great value. At the Home for Hebrew Infants the active immunization of all children showing a positive Schick reaction has prevented the development of any case of diphtheria for three years, although before these injections were used there had been yearly epidemics with the accompanying loss of several lives. The fact that there were during the first two of the three years a number of carriers of diphtheria bacilli among the youngest children adds to the proof that the prevention of diphtheria has been due to the immunizing injections. The practice has been to do a Schick test every three months and to only immunize the infants after they lost the immunity acquired from their mothers. This, probably, is the best practice for institutions where a bacteriologist is constantly on duty. Otherwise, it may be more sensible to inject all of the infants so as not to be liable to outbreaks occurring in those who have lost their immunity.

At the present time active immunization is being practised quite largely in the United States Navy and, to a considerable extent, in the Army. Although with antitoxin available death in an adult from diphtheria is rare and should never occur, nevertheless, under the conditions in military service the presence of a

few cases of diphtheria, with usually a number of diphtheria carriers on a vessel or in a concentration camp, creates a difficult situation to handle. By Schick-testing the men and giving the immunizing injections to those who react positively protection can be granted, and diphtheria made to cease as either a menace or an annoyance.

It should be noted that the development of immunity, either from natural means or through injections of toxin-antitoxin, or through injections of antitoxin, in no way prevents a person becoming a carrier, and that a carrier can, as any other individual, develop an ordinary follicular or croupous tonsillitis or pharyngitis. A case, therefore, that has a negative Schick reaction—*i. e.*, a person who possesses antitoxin and develops a suspicious throat, and a culture shows diphtheria bacilli—is no more a case of diphtheria than a person developing similar lesions who has no diphtheria bacilli. In one case we have an infection in a person who is a carrier of the bacilli, and in the other a person who is not. We are so apt to think that a positive culture in a suspicious throat proves that the lesions are due to the diphtheria bacilli lodged thereon that we forget that a carrier is just as apt to be infected with pyogenic organisms as one who is not. Frequently in scarlet fever patients in our hospitals croupous tonsillitis develops. Among these are some who have been immunized with antitoxin and others who are naturally immune, as shown by the Schick test. In all of these we realize that the individuals have antitoxin, and we find that without injections they recover just as well as with injections. We have never had a person with a negative Schick reaction develop the characteristic symptoms of diphtheria. It is certainly impossible for any person with antitoxin to be constitutionally poisoned by diphtheria toxin. Observations indicate that not even the superficial epithelium in these immune persons is poisoned by the diphtheria toxin made by the bacilli in carriers. It is absolutely proved that this does not occur to an extent which is characteristic of diphtheria. While a negative Schick test demonstrates that a person is safe, a positive reaction does not prove one is necessarily at the time susceptible, as there is, as in other infections, bactericidal immunity. The

recovery in most cases of diphtheria is due to the development of bactericidal and not antitoxic immunity

#### RESULTS IN FIVE REPRESENTATIVE INSTITUTIONS

Institution.	Number of susceptible children given toxin-antitoxin injections remaining under observation.	Period of observation. Months.	Percentage remaining immunized.
1	84	24	97
2	74	22	97
3	106	24	97
4	42	22	92
5	150	13	95

The results obtained are given so that the actual development of an immunity following either two or three injections can be seen. In all the other ten institutions similar results were obtained. Others added later will only become of importance when sufficient time has elapsed to test the persistence of the immunity



## CLINIC OF DR. FREDERICK TILNEY

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### WILSON'S DISEASE—PROGRESSIVE LENTICULAR DEGENERATION<sup>1</sup>

Essential Pathologic Findings. Historic Points, Work of Samuel Alexander Kinnear Wilson. Case Report Personal and Family History, Onset of Illness, with Symptoms, Physical Examination, Laboratory Tests, Development of Symptoms, Death. Discussion of Differential Diagnosis Postmortem Findings. Prognosis in Wilson's Disease

THE subject of today's lecture is progressive lenticular degeneration, a pathologic condition of the brain known as Wilson's disease, in consequence of the brilliant investigations published by that English writer in 1912. From the pathologic standpoint Wilson's disease is characterized by a remarkable coincidence of morbid changes in the liver and corpus striatum. The explanation of this simultaneous hepatic and cerebral involvement is still being sought, while the symptom complex, arising apparently as a direct result of the alteration in the lenticular nucleus, has stimulated a renewed interest concerning the nature and function of the corpus striatum, that part of the end brain which continues to invite the interest of the investigator as much as it perplexes the clinician.

Historically, it is interesting to note that the syndrome had been recognized as such long before the significance of the malady was suspected. As early as 1854 Frerichs gave the first exact description of Wilson's disease as we know it today in a treatise

<sup>1</sup>Lecture delivered to the Fourth Year Class of the College of Physicians and Surgeons New York, May 1918.

on diseases of the liver Frerichs' case was a boy ten years of age who developed at this time of life dysarthria, dysphagia, weakness of the limbs and tremors, while later on he became greatly emaciated and manifested a striking slowness in all of his movements without, however, the presence of any paralysis in the strict sense. In addition to these motor changes the patient showed a marked loss of facial expression. At no time during the course of the disease was there any involvement of sensibility and no evidence was elicited showing disease of the liver. Upon autopsy, however, an extreme hepatic cirrhosis was found which was reported as the sole pathologic finding in this case. Clearly, then, Frerichs had recognized most of the clinical symptoms which go to make up the syndrome of Wilson's disease. Moreover, he discerned one of the essential features in the pathology, namely, the hepatic cirrhosis. What he failed to observe, however, was the condition of the corpus striatum.

Many years passed before a similar case appeared in the literature, for it was not until 1888 that Gowers published a complete description of all the symptoms observed in progressive lenticular degeneration, calling the condition *létanoid chorea*. He also made note of the changes in the liver, but it was not until several years later that he was struck by the fact that these hepatic changes were associated with what appeared to be a disease of the extrapyramidal system. A short time after the publication of this case a sister of this same patient came under Gowers' observation suffering from identical symptoms. This gave color to the supposition that the disease was probably familial and possibly hereditary.

It remained for Wilson to collect from the literature some 12 cases and, from personal observations of his own, to show that there is a disease pathologically characterized by the simultaneous involvement of the corpus striatum and the liver, occurring in childhood or adolescence, having a familial tendency and consisting of the fairly well stereotyped group of symptoms which distinguish it.

The patient whose history is here presented is one of the

few cases upon which there has been opportunity to make extensive study in this country. He was a Scotch boy, fifteen years of age, and was admitted to the Presbyterian Hospital because he suffered from a stiffness and trembling of the right arm, together with difficulty in speaking. Whenever the patient attempted to use his right arm for any purpose the hand trembled so that it was almost impossible for him to perform any skilled act.

This boy came to the United States when he was four years old, since which time he lived in New York City. Until his present illness he was considered a healthy and a normal boy. His school career was good. He was considered bright and graduated from grammar school at eleven years of age. His previous history shows little of moment. He had measles and scarlet fever when he was eight years old, but made a good recovery from both these illnesses. When he was ten years old he was operated on for the removal of tonsils and adenoids because of some respiratory disturbance, and thereafter was not subject to sore throat or any sort of sickness. He had no bad habits and his general physiologic status was good, he slept and ate well, his bowels were regular, and his weight was normal.

The family history of this patient should be scrutinized with more than usual care, knowing as we do the familial and perhaps hereditary tendency of this disease. The boy had two brothers and a sister younger than himself. All of them, up to the time of his death, were in good health and have remained so to the present time. There is no history of any similar illness in the family of either parent, nor, indeed, is there any record or recognition of family nervousness or neuropathic tendency. There is no history of syphilis, deafness, blindness, alcoholism, or feeble-mindedness in the direct or collateral branches of the patient's family.

The first indication of the illness which ultimately caused the patient's death made its appearance in August, 1912, when he began to notice a change in his control of his right hand. There was apparently no cause for this at the time. He complained that his fingers and forearm shook when he tried to write or to



button his clothes. This shaking was not confined to the right hand, for when he was excited or fatigued both hands trembled and the arms grew stiff. He was sent to Canada in December, 1912, in the hope that a change of climate would improve his condition, but during the nine months of his sojourn there no perceptible change could be noted. In fact, he seemed to grow progressively worse.

Upon admission to the Presbyterian Hospital in August, 1913, the stiffness had extended from the arms to his entire trunk musculature as well as to his legs. There is some evidence that he may have had a slight convulsive seizure before entering the hospital, but, as this occurred at night and as no similar attack was observed during the course of the disease, it is open to question whether the boy suffered an actual convulsion.

Another striking feature at this time was the boy's facial expression. The muscles of his face had become stiff, so that his mouth gaped widely most of the time, giving him a stupid appearance. At intervals he would give voice to a sound not unlike the cry of an animal. This was high pitched and explosive in character. It did not denote any emotional change in the patient, nor was he cognizant of any provocation.

Neurologic examination made at the time of his entrance to the hospital was as follows:

Co-ordination showed no marked disturbance either equilibrium or non-equilibrium. Later, when the muscles became rigid, it was difficult to estimate the state of his co-ordination.

Skilled acts showed no *adiadokocinesis* or *dyssynergia*. There was no *apraxia*, *dyspraxia*, or *aphasia*. The patient could move either arm at will, and oftentimes with much force. There was no demonstrable paralysis. Pronunciation became progressively more difficult until finally a well-marked *dysarthria* was present.

All of the deep reflexes were equal and active on the two sides. There were no pathologic reflexes present. The superficial reflexes were present and active on the two sides. There was no *Babinski*, *Chaddock*, *Oppenheim*, or *Gordon*.

Aside from the questionable convulsion previously referred

to, the only other abnormal involuntary movement present was the tremor, which has also been referred to. This was most marked in the hands, but could be observed in the forearms and arms, as well as in the tongue. Its rate was 5-6 per second, it was rhythmic and of relatively small amplitude. Action and emotional influences increased it, but it disappeared during sleep.

The muscular strength at the time of entering the hospital was full, but subsequently it decreased rapidly. There was no change in the volume of the muscles nor in the contour of the parts. The entire somatic musculature seemed denser because of the rigidity. The electric reaction was normal. The myotatic irritability showed some increase, but the nerve status was normal.

The general sensory examination showed that all qualities of sensibility were normal.

All of the cranial nerves were normal with the exception of the facial, glossopharyngeal, and vagus. The facial muscles were rigid and gave the mouth a gaping appearance. There was considerable dysphonia and a progressive dysphagia.

The laboratory tests of the blood, spinal fluid, urine, and feces were negative. The carbohydrate assimilation test showed nothing abnormal.

In the first days of the patient's stay in the hospital he was able to walk about with assistance, but his arms and legs were held in the rigid attitudes shown in Fig. 1. In attempting to walk, the stiffness of his calf muscles caused him to stand upon his toes. This gave him a digitigrade progression. The muscular rigidity was present in any posture which he might assume. In sitting down the feet were held rigidly flexed upon the legs, the legs upon the thighs, and the thighs upon the pelvis (Fig. 2). The arms were also held in contracture like attitudes, the left one being rotated internally, with the forearm extended on the arm, while the right was flexed upon the forearm, and the fingers, more especially the index and thumb, were in flexion at their proximal joints. The right arm was rotated internally and abducted slightly, the forearm was flexed

upon the arm, and the fingers and wrist resembled in their contractural postures the malattitudes of the right side

The slightest force applied to his body would cause him to fall backward, and in doing so it seemed as though his whole body moved as a single piece. When recumbent (Fig 3) he



Fig 1—Showing malattitudes in standing



Fig 2—Body held rigid in sitting posture.

chose to lie upon one side or the other, with the legs and thighs in flexion

It will be remembered that the patient gave as his first complaint a stiff shaking of the right arm and hand, and this early symptom soon became one of the conspicuous features of the disease. The tremor had many characteristics which allied it to the tremor of paralysis agitans. It was manifest in the

small muscles of the hand and in the forearm and arm. In its type and form it was monomorphous, that is to say, it always had the same rhythm and general character, although its amplitude increased during motion of the arm. At such times also there was a distinct increase in the force of the tremor. It is to be noted that this tremor, so like that of paralysis agitans in many of its features, differed in this one fundamental respect, namely, that it was increased by action and decreased by rest, and, furthermore, emotional disturbance of any kind served to make the amplitude of this tremor greater.



Fig. 3—Attitude assumed when recumbent.

One remarkable factor about this change in the muscular system of the patient was the surprising absence of any true paralysis. The voluntary control of the muscles, although it was difficult, was nevertheless preserved. The patient could move his arms and legs at will, but each of his efforts gave the impression of a volitional exertion struggling against the resistance of his muscular rigidity.

At the end of several weeks the patient began to experience difficulty in swallowing and his speech became more difficult to understand. The increased rigidity of the muscles about his lips made his mouth gape still more widely, causing him to

would seem to be an argument against this disease. While there is authentic record that multiple sclerosis may begin in childhood, nevertheless such cases are extremely rare. This diagnosis, therefore, deserves attention only if the symptom complex itself is sufficiently convincing to dispel doubt. But that is not the case with this boy, for here we have few if any of the well-recognized symptoms of the disease. Unquestionably, the spasticity, the rigidity of the muscles, might well enough be the result of multiple sclerotic changes, on the other hand, not a single one of the classical triad of Charcot is present. There is, for example, no nystagmus, no scanning speech, and certainly the tremor was not of the intention type, since it was present both in action and inaction. Furthermore, to substantiate the diagnosis of multiple sclerosis, the degree of rigidity of the muscles presented by this patient should have been accompanied by some pronounced change in the deep and superficial reflexes, but such changes were absent. There was no Babinski and no conspicuous increase in the tendon reflexes. The abdominal reflexes were present. Investigation of the fundus shows an absence of the bilateral temporal pallor which has come to be regarded as such a significant feature in multiple sclerosis. Thus, the age of the patient is not alone against this diagnosis, but there is nothing in the symptom complex which would seem to uphold such a conclusion.

Considering *paralysis agitans*, certain features about this boy's condition certainly suggest this possibility, although complete analysis shows this diagnosis is untenable. In the first place, the age of the patient presents a difficulty, since we are accustomed to associate the Parkinsonian syndrome with adult life. This, however, need not prove an insurmountable obstacle to the diagnosis, particularly as the recent work of J Ramsay Hunt has called attention to a juvenile form of *paralysis agitans* which he attributes to an abiotrophic disorder affecting the globus pallidus of the lenticular nucleus. But we must also take into account the type of motor defect exhibited by this patient, particularly the tremor. While it has much in common with that of Parkinson's disease, there are, neverthe-

less, features about it which cannot fail to mark it as strikingly different. Thus, the tremor is one of inaction, but its range and force and amplitude are alike increased by action and emotion. This is totally different from the tremor of paralysis agitans, which tends to subside, if not disappear altogether, during action. Again, the rigidity of the muscles has something in common with paralysis agitans, but there is a difference, not only quantitative but qualitative. In Parkinson's disease there is little tendency toward the production of malposition in the extremities, whereas in Wilson's disease the rigidity of the muscles is so great as to produce marked malposition in the fingers, hands, and arms, and in the feet and legs. The characteristic tendency of Parkinson's disease to produce certain well-defined changes in facial expression and in bodily attitude are absent in Wilson's disease, in which, though it may undergo marked alteration, the facial expression has none of the wax mask character so common in Parkinson's disease in which the stolid and inflexible expression is quite different from the almost idiotic one seen in progressive lenticular degeneration because of the more or less widely gaping mouth.

In regard to *pseudobulbar palsy*, particularly of the bulbar type, some features of this case may be considered to warrant this diagnosis. One of these features is the emotional instability, and particularly the sharp cry which the patient occasionally uttered. Others are the dysarthria and the dysphagia which he manifested. But it will be remembered that there was no actual paralysis in the muscles of phonation nor in those of deglutition, so that the difficulty in articulation and in swallowing could not, in the strict sense, be attributed to a supranuclear lesion. The explanation of these disturbances is rather to be found in the hypertonicity of the muscles, one of the outstanding features of Wilson's disease. Therefore, to regard this clinical picture as due to pseudobulbar palsy would at once imply certain contradictions in our fundamental conceptions of the nervous system, for it would be necessary to attribute the hypertonicity, in this light, to an affection of the pyramidal tracts. It is impossible to suggest such an involvement in the

absence of the almost invariable pyramidal tract symptoms, such, for instance, as the Babinski reflex, increased tendon reflexes, ankle-clonus, and abolition of the abdominal reflexes. This possibility, therefore, is too remote to receive more than cursory attention.

In regard to the *pseudosclerosis*, certain features would eliminate this possibility. One characteristic of this involvement of the nervous system makes itself apparent in a yellow tinging of the sclera, and the absence of such pigmentation in our case is a significant argument against this diagnosis. This argument becomes conclusive through the fact that in the *pseudosclerosis* mental symptoms of a more or less severe grade, even to the extent of actual dementia, are present. It was notable, in our case, that the boy's mind remained normal until a few days before his death.

I think there can be no doubt, after reviewing these several possibilities in the differential diagnosis, that it would be difficult to arrive at any conclusion other than the diagnosis offered in explanation of this unusual and extremely interesting clinical condition.

In order to put the matter to the final test, we are fortunate in having the pathologic material obtained from a complete autopsy, and since then carefully studied. As has already been stated, it was impossible to make the definite diagnosis of Wilson's disease without postmortem findings, for the *sine qua non* of this diagnosis is a hypertrophy of the liver. In this case, macroscopically, the liver showed a marked *cirrhosis*, illustration of which is shown in Fig 4, and the microscopic sections revealed the following. Varying amounts of edematous connective tissue, in which there are small wandering cells, fill the portal spaces. There are great numbers of regenerating bile-ducts and many capillaries. At the periphery of the lobule new forming bile-ducts are seen and they are also to be found penetrating the lobes. There are narrow bands of connective tissue between most lobules, and masses of connective tissue entirely surround an occasional remnant of a lobule, though most of the lobules are not reduced in size. There is, however,

the greatest difference in their appearance. In the greater number a cloudy swelling marks the liver cells, blue granules are found in the cytoplasm, and the nuclei, though not enlarged, stain deeply. In other lobules there is a moderate amount of fatty infiltration, particularly at the periphery. The cytoplasm is swollen and granular, a considerable number of nuclei cannot be seen while the remaining ones, in general, stain irregularly



Fig 4—Cirrhosis of the liver

and are swollen. The lobules which show only cloudy swelling are adjacent to the degenerating ones. There is some evidence of regeneration of the liver cells, at the periphery of the lobules especially (Figs 5 and 6).

*Microscopic Appearance of the Central Nervous System*—Upon macrotomic section the central nervous system, with one exception namely, the lenticular nucleus on both sides, appeared normal. There were no gross lesions discernible in the

<sup>1</sup> From Neurological Bulletin of Columbia University, June 1918.



cortex or medullary substance. The internal capsule showed nothing demonstrable in the gross. The midbrain, pons and isthmus, cerebellum, and spinal cord were normal. The coverings of the brain showed no pathologic condition.

Upon inspection of the macrotomic sections in the gross, those containing the lenticular nucleus showed that this part of

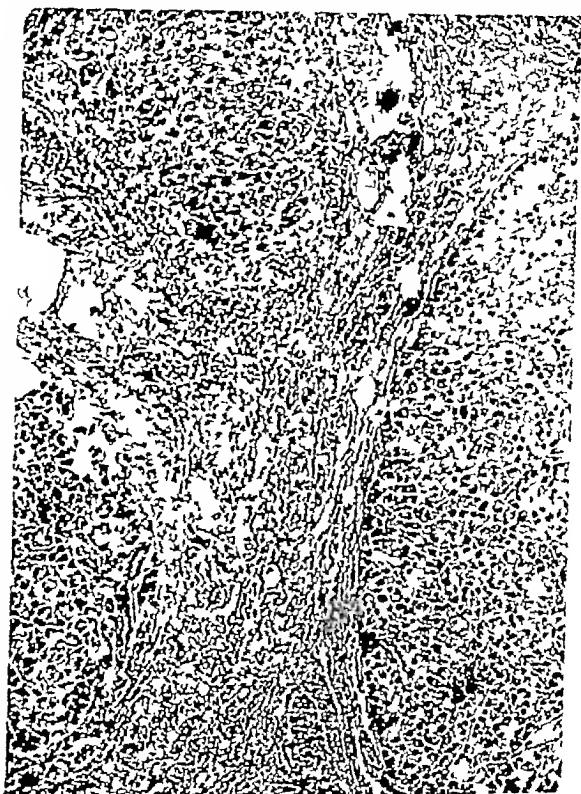


Fig 5 —Hepatic hyperplasia

the corpus striatum was the seat of some pathologic change. The lesions were minute and gave the putamen a spongy appearance. This was more particularly true in the dorsal or superior portions of the putamen and was likewise more pronounced in the region bordering upon the retrolenticular por-

tion of the capsule than in the areas contiguous to the anterior limb of the capsule. Microscopic study of the brain led to the following conclusions:

The cerebral cortex in all areas was normal in its cellular content and in its fasciculation. The vascular status showed no

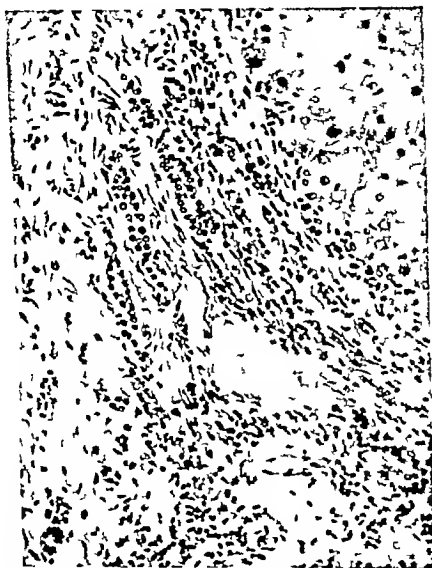


Fig. 6.—Character of cellular changes in the hepatic cells and also the proliferation of the bile-ducts.

pathologic alterations. The corona radiata and the centrum ovale as a whole were normal. The thalamus and hypothalamus showed no changes except that in the latter there was an apparent attenuation in the bundles of fibers which go to make up the ansa lenticularis. The infundibulo-mammillary region

was normal, the hypophysis in its glandular and neural portions showed no abnormal changes. The epithalamus, including the habenular region and the epiphysis, were normal. The metathalamus showed no alteration. There was no evidence of degeneration in the fibers of the midbrain and it was difficult to discern any appreciable change in the nucleus ruber. The isthmus, pons, cerebellum, medulla, and spinal cord revealed no pathologic alterations in their cell constituency or nerve-fibers.

The microscopic appearance of the lenticular nuclei of both sides was striking. Such pathologic changes as one noted were confined to the putamen and were more pronounced in the regions of this structure already mentioned in the description of the gross alterations.

*A The Cells in the Putamen*—The larger pyramidal elements, especially, showed a marked degeneration, in some places these cells had been entirely destroyed, leaving in their place a number of lacunæ about which were collected ameboid glia cells and other cellular elements which were regarded as plasma cells. In the areas where many of the nerve cells had disappeared in this manner, the putamen gave the impression of a beginning cavitation as illustrated in the accompanying photomicrographs (Fig 7). In many regions the smaller pyramidal cells, as well as those of the larger variety, showed definite tendencies toward degeneration. Their nuclei were eccentrically placed, the cells appeared swollen, and their tigroid bodies were difficult to distinguish. From the general picture of the cellular alterations it seems fair to conclude that a diffuse parenchymatous degeneration was in process of development throughout the entire putamen. In the areas where it had reached its greatest intensity a process of cavitation had already been established.

*B The Fibers of the Putamen*—Even in the Pal-Weigert preparations it was difficult to detect any marked degree of fiber degeneration, although in some places there seemed to be a decrease in the myelin sheaths of some of the axis-cylinders.

*C Neuroglia*—Throughout the entire lenticular nucleus there was a marked degree of gliosis. This reached its greatest intensity, however, in the putamen, the latter standing out in

marked contrast to the head of the caudate nucleus, which appeared to present no change in the neuroglia.

*D* Blood vessels and Perivascular Spaces —Throughout the entire extent of the putamen the blood vessels seemed to have shrunk away from the adjacent tissue and to be surrounded by

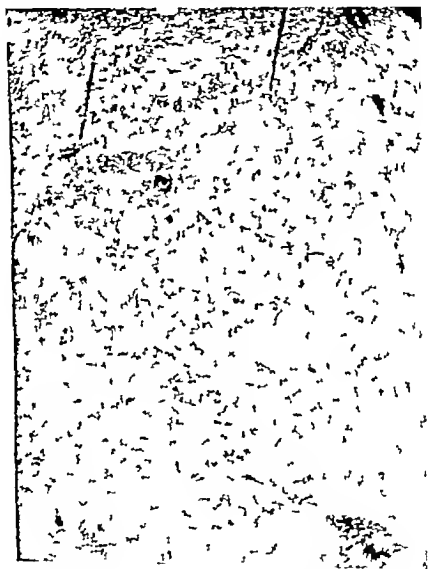


Fig 7 —Gliosis in the putamen and beginning cavitation.

large, irregular spaces (Fig 8). These, however, must not be considered as perivascular lymph-spaces and, indeed, it is doubtful whether they are of moment in the pathologic process at all. They may well be artifacts and are simply mentioned in this connection as their occurrence has been noted in the pathologic observations of other reported cases. One reason for making it

seem likely that these irregular spaces are artifacts is that their occurrence in this particular brain is not limited to the lenticular nucleus, but rather diffusely scattered throughout several parts of the central axis. The perivascular lymph-spaces were not distended nor did they contain any cellular elements which might be considered abnormal, either in amount or character.

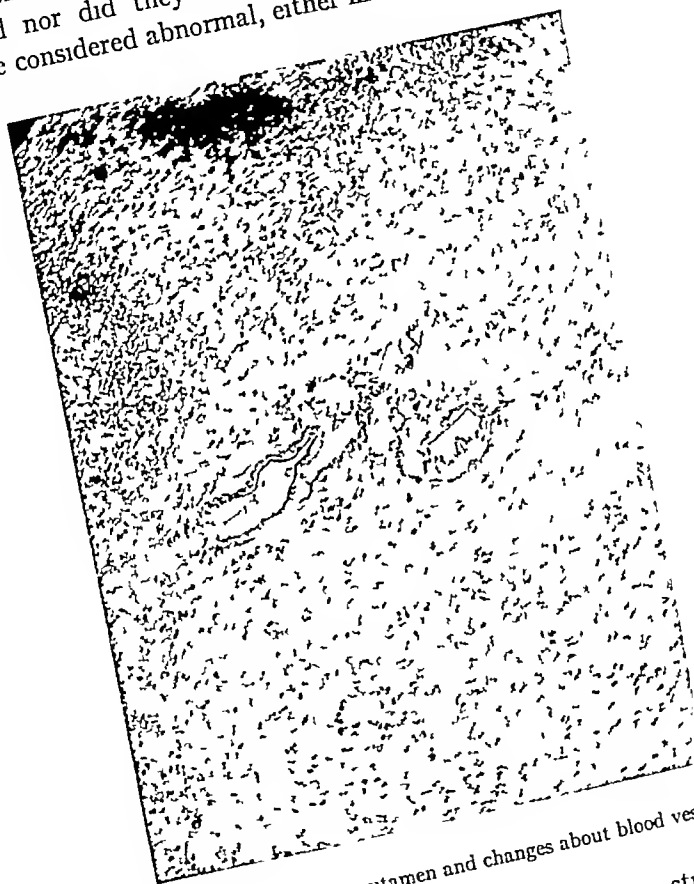


Fig 8—Ghosis in the putamen and changes about blood vessels.

The conclusions drawn from the pathologic study of this brain are that the lenticular nuclei of both sides were in a state of degeneration which probably was progressive. No portion of the brain showed any unusual biliary or other type of pigmentation.

Clinically, there are two distinct types of this disease one *acute* or *subacute*, the other *chronic*. The two types differ very little except in the rapidity with which the invariably fatal termination occurs. The acute cases are apt to have some febrile disturbance, their duration is usually four to twelve months. The chronic cases may last from one to four years after the first appearance of the symptoms.

The striking and characteristic symptoms of the disease are disturbances of motor function.

1 *Tremor* is one of the outstanding features. It is usually one of the earliest and one of the most marked symptoms. It is increased by excitement, or if attention is drawn to it, or by voluntary effort. The range is apt to be fine, at least at the outset, but with volitional movement the excursions become wider. In the advanced stages it involves the head and trunk as well as the limbs. It disappears during sleep.

2 *Spasticity* or, better, *hypertonicity* is the second of the cardinal symptoms. Beginning in the limbs, it later spreads to the rest of the voluntary musculature, with one solitary exception—the extrinsic ocular muscle. Their movements remain quick and free. If one takes hold of one of these hypertonic arms or legs and tries to impress on it alternating flexion and extension, he is at once conscious of a considerable degree of resistance in the opposing muscles. It evidently consists in a generalized condition of increased tone in all the muscles indiscriminately.

Every patient reported has shown contracture, usually with the flexion contracture accentuated. This symptom is merely a result of the hypertonicity.

3 *Dysarthria* and *dysphagia* are almost invariably present. They, like the contractures, are the result of the hypertonicity. The dysarthria is characterized by the slurring element without the staccato element of disseminated sclerosis.

4 *Muscular weakness* and *emaciation* develop, associated with the contractures and immobility of the limbs. A considerable degree of voluntary power, however, has remained in the majority of cases. The weakness and wasting of the muscula-

ture are doubtless due in part to the atrophy of disuse and in part to the disturbance of metabolism

5 The symptoms so far enumerated have all dealt with motor disturbances. Sensory symptoms, except for pains in the limbs mentioned in some cases, have not been observed. Examinations failed to reveal any change in sensibility, nor has any definite alteration of the tendon or cutaneous reflexes been found. Toward the end of most of the cases, however, it has been recorded that the organic reflexes became impaired. This Wilson attributes partly to mental deterioration, partly to loss of voluntary control over the muscles. His efforts to find a lesion in the cord were quite negative.

6 *Psychical symptoms*, though present in some form in most of the cases, have been very variable. Simple-mindedness, failure of memory and of mental powers, emotionalism, change in disposition, transient delusions, hallucinations of hearing, excitement, narrowing of the mental horizon, facility, docility, and childishness are some of the terms used to designate the mental disturbance. Attempts to classify these symptoms have been fruitless, but it seems probable that some psychical disturbance forms an integral part of the clinical picture.

7 *Significant negative signs* are the following: the optic disks and pupillary reactions are normal, there is no nystagmus, there are no cerebellar symptoms.

Concerning the etiology and pathogenesis of the disease there are some features worthy of note.

1 *Age*—Progressive lenticular degeneration is a disease of adolescence and youth. The age of the youngest was ten years at the onset, of the oldest, twenty-six years. The average age is about fifteen years.

2 *Sex*—Males and females are about equally affected. It is worthy of note that in the reported cases, menstruation, if established prior to the onset of the disease, almost invariably ceased. The significance of this is obscure.

3 *Heredity*—Records of family nervous disease or neuropathic tendencies are not found in the reported cases. About

three-fourths of the cases are familial. There are two reports of three cases occurring in children of the same family.

4. No constant so-called *predisposing causes* are evident in the histories.

It has been suggested that the disease is an expression of a degenerative tendency—an abiotrophic defect—but it is quite striking that the observers of the reported cases almost uniformly have stated that their patients had normal mental and physical development prior to the onset. It seems highly improbable that a congenital tendency to degeneracy should lie so completely latent for twelve, fifteen, or twenty years.

Speculation as to the intimate nature and pathogenesis of the disease is perhaps interesting, but in the light of the available facts and absence of experimental proofs, rather fruitless. There are one or two philosophic considerations, however, which are worthy of note. There seems to be no analogy for such a distinct morbid entity whose most striking characteristic is a specific association between disease of one of the viscera and disease of a particular part of the gray matter of the central nervous system.

In any discussion of the etiology syphilis must be considered. Most of the cases recorded occurred in the pre-Wassermann days, but the observers were on the alert to discover signs of syphilis and the absence of positive evidence of either acquired or inherited syphilis is striking. In the more recently reported cases, unquestionably conforming to the syndrome, the Wassermann has been negative. Homén made specially exhaustive efforts to prove that his three cases were syphilitic, but despite his conclusion that they were probably of the nature of a so-called parasymphilitic condition, he specifically states that positive evidence of syphilis, either in parents or children, was wanting. Moreover, the cirrhosis differs from that of hepatic syphilitic cirrhosis in children. The latter is quite constantly associated with ascites.

Alcohol could not be shown to have played a part in the etiology. The presumption, therefore, arrived at by Wilson is that the disease, although familial, is acquired and is toxic in



origin, and that the toxin has a selective action on the lenticular nucleus. A very significant analogy to such a hypothesis is furnished by the observations of Werneke, Schmore, Esch, and Pfannenstiel who have described cases of icterus gravis or neonatorum. This disease is familial, occurs in the earliest days of life, and is fatal in a very short time, the infants rarely living more than a week or two. The interesting feature is that in addition to the general bile-staining of the tissues of the body, there is a selective action in the cerebrum and central nervous system. The lenticular nucleus, the corpus Luysi, the cornu ammonis, the dentate nucleus and the olives, the sensory nuclei of the medulla and pons are specially singled out and stained a bright yellow. The corpus Luysi and lenticular nucleus stain with the greatest intensity. Microscopically, the bile pigment is found in the bodies of the nerve cells. The patients, however, show no symptoms referable to the nuclei. In ordinary cases of jaundice in older people from whatever cause, and in jaundice of congenital bile-duct obliteration, no such selective staining of the gray matter has ever been observed as taking place.

As to the prognosis of the disease, all of the cases reported up to this time have proved fatal in one to four years. Treatment is unavailing in the cure of the condition. It is, therefore, confined to palliative therapy and symptomatic relief.

CLINIC OF DR. WALTER L. NILES

BELLEVUE HOSPITAL

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SUBACUTE NON-TUBERCULAR PULMONARY ~~INFLAMMATION~~

Three Illustrative Cases, with Differential ~~Diagnosis from~~  
Tuberculosis Management and Treatment.

On March 20, 1918, he had been feeling quite as well as usual, except that during the previous three weeks he had a cough, which was evidently not very severe and was unaccompanied

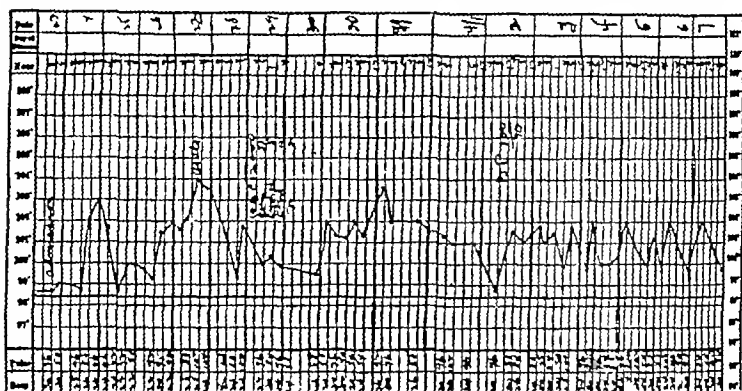


Fig 9—Chart of Case I

by sputum, when he was seized with a very severe pain in the left side of his chest. He had no chill and at that time was not conscious of fever. The cough became aggravated, but there was still no sputum, and, indeed, at no time has he had

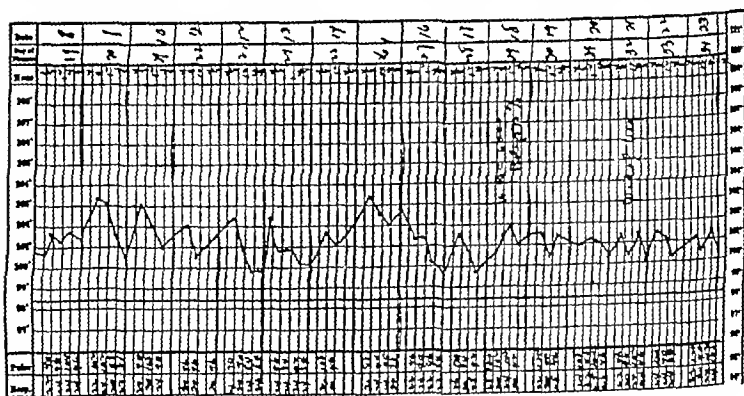


Fig 10—Chart of Case I

but very little, it having been difficult to get proper specimens for examination. He does not recall that the pain was aggravated by the cough or by deep breathing. He thought that he had

lost about 5 pounds in weight during the three weeks which he had coughed. At the time of admission he felt comfortable except for a sense of discomfort in the region of his left hypochondrium and feverishness.

On referring to his chart (Figs 9-11), you will notice that his temperature was practically normal on admission, but it soon rose, and since that time he has had more or less fever, which has generally been quite continuous in type, with a very gradual deferescence until the present, when it has almost reached normal. During all this time his respirations have been increased scarcely at all and his pulse has been just about in proportion to his

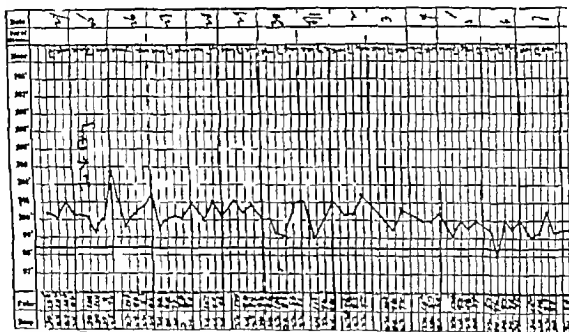


Fig 11 — Chart of Case I

temperature, very rarely faster and frequently distinctly slower. What little pain he had quickly subsided, and most of the time he has said that he felt perfectly well. He has coughed very little at any time and during the past two weeks has rarely coughed at all. Such specimens of sputum as we have been able to collect have showed a variety of organisms on examining smears. On culture, the predominant organism has in each instance been a pneumococcus, Type IV, accompanied by non-hemolytic *streptococci* and *Micrococcus catarrhalis*.

On the day after admission his leukocytes were 12,000, with 81 per cent of polymorphonuclear cells and 8 per cent. of

lymphocytes That is the highest count which has been observed One taken yesterday showed 6000 leukocytes, with 75 per cent of polymorphonuclears

He is, as you see, well nourished and has maintained his muscular development surprisingly well He has at no time looked very ill, his tongue has been moist, and his cardiovas



Fig 12—Case I Scattered areas of infiltration throughout the left lower lobe

cular and gastro-intestinal systems have been perfectly satisfactory Examination of his chest was entirely negative except for a small area over the middle of the left lower lobe posteriorly, where there was a moderate impairment of resonance, a slight increase in fremitus, rather soft, low-pitched tubular breathing, and a great many fine and medium sized moist râles The signs are now exactly the same, except that the

râles are somewhat less numerous and a little drier in quality

Fearing that he might possibly have an empyema, a needle was introduced, but no fluid was obtained

We have twice had his chest x rayed and the plates are before you. You will notice that there is quite a large area in the lower portion of the left chest where the density is decidedly increased. This area is quite irregular in outline, varies considerably in density in its different parts, and is rather spotted. It does not, however, have the appearance of a tuberculous lesion, several examples of which I have recently shown you. Dr. Hirsch thinks there is some evidence of cylindric bronchial dilatations, particularly at the points indicated by the arrows. Elsewhere the lungs are perfectly normal in appearance (Fig. 12).

CASE II.—The next patient, a colored boy eighteen years of age, was admitted to the hospital on April 2, 1918, complaining of fever.

He says that his father died at about fifty after one year's illness, the exact nature of which he does not know. Of course, tuberculosis is to be suspected with such a history, particularly in a colored person. His mother is, however, alive and well and he has four brothers and four sisters, all of whom are perfectly healthy. One brother died from an accident at eight years of age.

He is employed as a laborer removing ashes from a factory. His habits have been good. His previous personal history is, however, of interest and very likely of significance. In 1911, while living in South Carolina, he was sick for three months with what he calls "typhoid pneumonia." He was in bed for two months. The onset was slow, he had a cough throughout the illness, and he recalls that he was greatly troubled by a pain in the left side of his chest. His sputum was never bloody. He apparently made a good recovery, but in 1913, when living in North Carolina, he had "malaria," which lasted for about three months. Again he coughed and had pain in his left chest throughout the illness. Since that time he has felt perfectly well, having had no cough or dyspnea and has maintained his usual weight.

The present illness began on March 26, 1918 The onset was gradual, with a feeling of general malaise, fever, and cough, which was accompanied by small amounts of white expectora

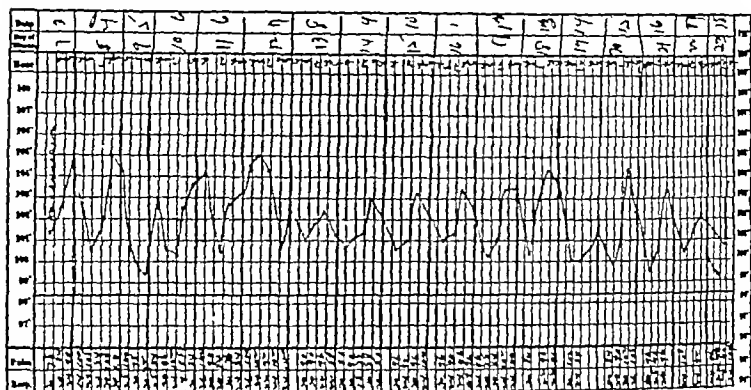


Fig 13 —Chart of Case II

tion He had been up and about until his admission to the hospital, being referred here from the Cornell Dispensary

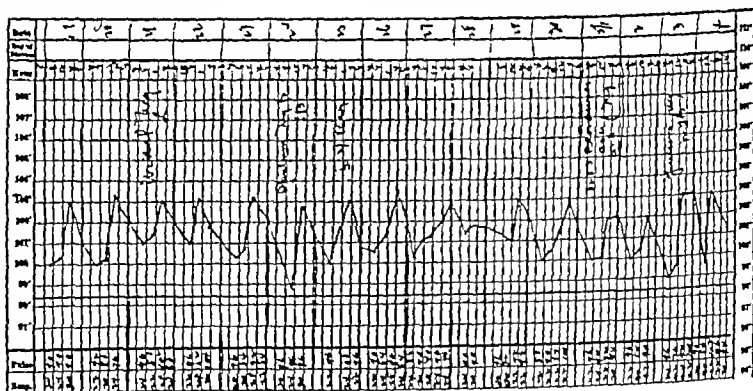


Fig 14 —Chart of Case II

Study of his temperature chart (Figs 13-15) shows that it has been much more irregular and has averaged somewhat higher than that of the last patient The tendency has lately been somewhat downward, though it reached 103.4 F yesterday

afternoon It is normal this morning He has had no chills or sweating His respirations have not been accelerated and his pulse has generally been rather slow in proportion to his temperature

Several blood examinations have showed 10,000 leukocytes as the highest count Yesterday the leukocytes were 8500, with 72 per cent. of polymorphonuclears and 26 per cent. of lymphocytes

Upon admission his physical examination was curiously negative I was unable to detect any abnormalities in his lungs, and it was not until after he had been here a week that I noted

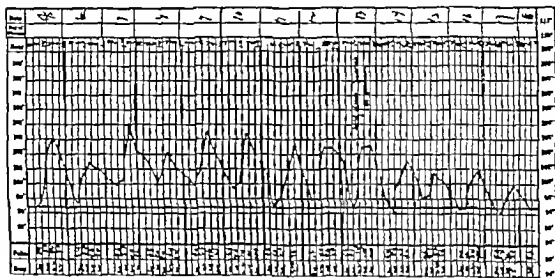


Fig 15—Chart of Case II

slight dulness and a few persistent fine crackling râles at the end of a deep inspiration over the left lower lobe Later quite large showers of crepitant râles were heard, yet there was no change in the breath sounds, neither was the fremitus modified These signs—dulness and fine râles—have persisted to the present time

We at first thought he certainly must have pulmonary tuberculosis That suspicion is, of course, always more pronounced when considering sick colored people, but in the absence of the usual manifestations of typhoid fever, together with negative blood-cultures and Widal reactions, it seemed quite justified despite the absence of physical signs and his slow



pulse Repeated examinations of his sputum have been negative for tubercle bacilli, though, of course, these negative findings do not rule out the disease. Cultures of his sputum have showed Type IV pneumococci together with *Micrococcus catarrhalis*.

Perhaps I should emphasize the fact that his blood Wassermanns have twice been negative, with both alcoholic and chole-

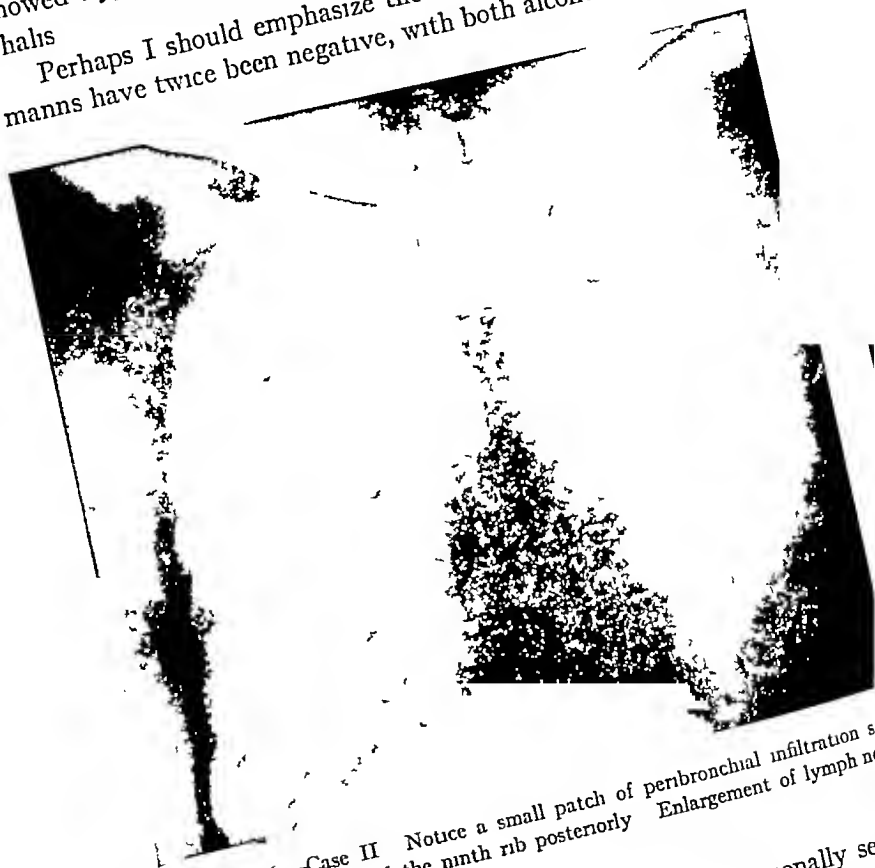


Fig 16—Case II Notice a small patch of peribronchial infiltration s. at the left base behind the ninth rib posteriorly Enlargement of lymph nodes at the roots of both lungs

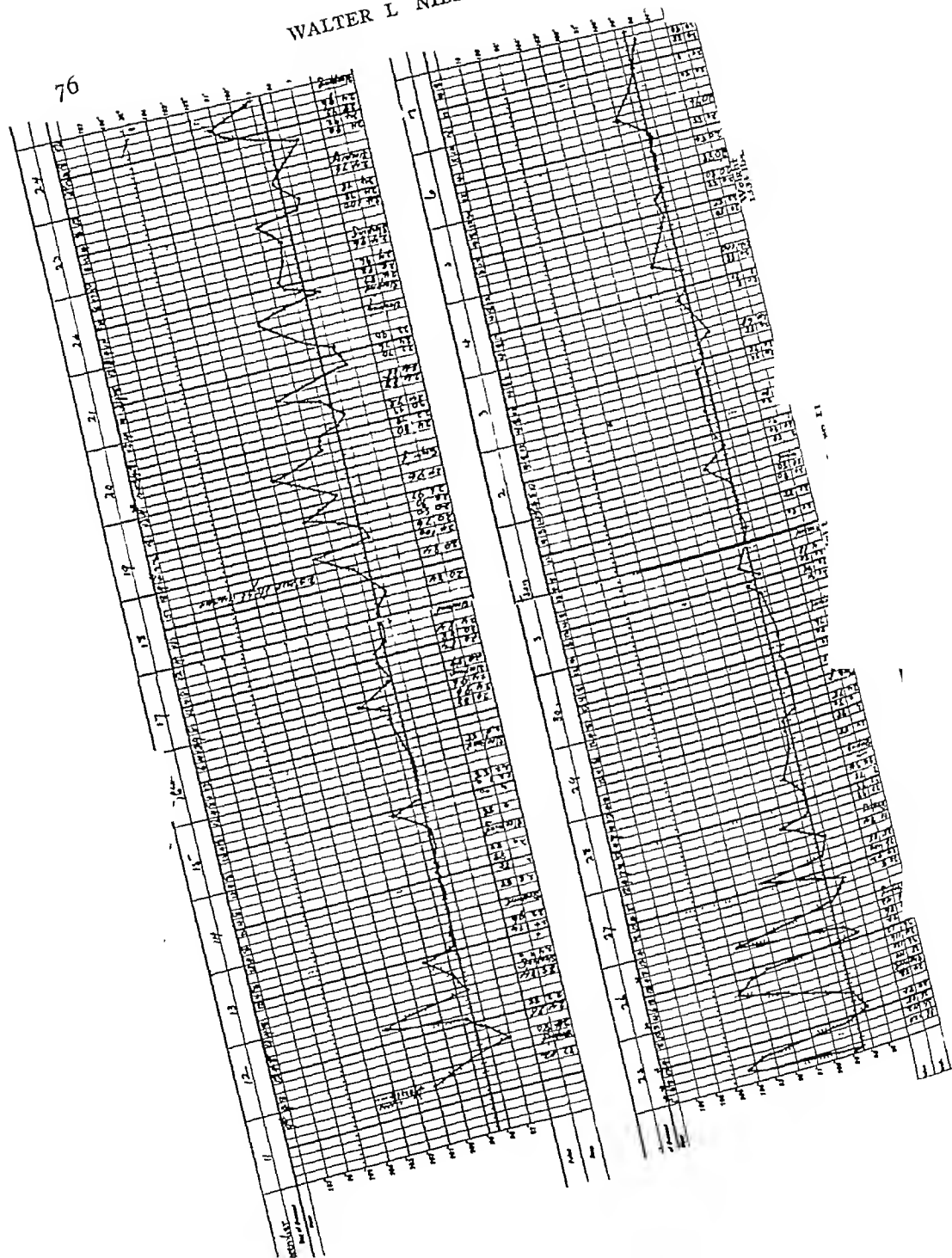
terminized antigens Syphilis of the lung is occasionally seen—we have recently had 2 cases—but I have never known it to be accompanied by so much fever as this boy has had. A radiogram of his chest is now before you (Fig 16) You will notice that there is an area of increased density which appar-

ently lies at the extreme base of the left lung. It extends downward in the direction of the bronchi and is probably evidence of peribronchial infiltration. This irregularity of shadow along the dome of the diaphragm is indicative of pleural adhesions, and you see there is a similar appearance on the right side as well. The mediastinal shadow is wide and irregular, especially at the roots of the lungs, and indicates an adenopathy of the mediastinal and peribronchial nodes. The upper lobes are perfectly clear and there is nowhere the appearance of a tuberculous lesion.

I think it is safe to say that this case is very similar to the previous one. The lesion is not quite so extensive, though the constitutional symptoms have been more pronounced. Yet the general picture is about the same.

CASE III --I have also brought the temperature chart (Figs 17-19) and radiograms from a similar case which I have been following the past winter. The patient is a man thirty years of age, and his history, which goes back to 1906, illustrates more diverse and extensive effects from an infection quite similar to the ones I have related.

He was always perfectly well until sixteen years old, when he had an attack of fever accompanied by pain in the right side of his chest, which was called "grip." It was not very severe and the temperature continued for only ten days. A week after its subsidence jaundice developed. This lasted for six weeks, during all of which time he coughed and had some discomfort in the region of his liver. He lost weight moderately, but apparently made a perfect recovery and was well for three years. His symptoms then became referable to his gastro-intestinal tract and were those of intestinal intoxication. His bowels became increasingly constipated and he suffered with frequent bilious attacks with headache. For three years he had various sorts of treatment, but got progressively worse, and in 1913 a laparotomy was done. It was reported that he had chronic appendicitis with adhesions, his appendix being removed and the adhesions liberated. He felt better for six weeks, at the end of which time his symptoms began to return,



and in a few months he was just as badly off as before. During the next four years he spent a considerable part of his time in various sanitariums. Gradually his symptoms became more definitely referred to his epigastric region, and in April, 1917, he was again operated. This time chronic cholecystitis with surrounding adhesions, which caused a partial obstruction of the duodenum, was revealed. There was also a band of adhesions extending from the gall bladder to the transverse colon. Numerous other smaller bands were found connecting coils of intestine, particularly in the liver region, the surface of which

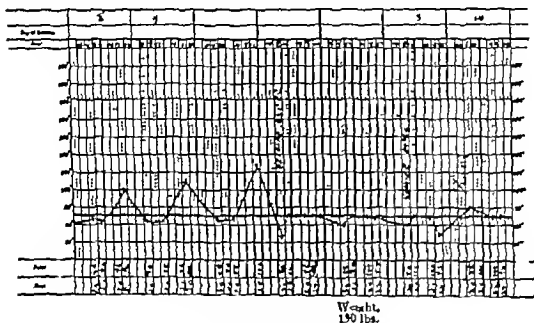


Fig 19—Chart of Case III

was lusterless and evidently thickened. He doubtless had a low grade of chronic peritonitis. Following this operation his abdominal symptoms improved somewhat.

In June, 1917, he had an attack of fever accompanied by a non-productive cough. He was then seen by Dr. James A. Miller, who radiographed his chest and had his sputum cultured. The cultures showed Type IV pneumococci and the radiograms showed thickening of the pleura over the bases of both lungs and some infiltration in the right lower lobe.

All during this period of four to five years he recalls occasional attacks of fever, which usually lasted only a day or two and which were ascribed to intestinal intoxication or "grip."

During the summer of 1917, while he gained a little in weight, the periods of fever became more frequent, and in September he developed a temperature of  $103^{\circ}\text{F}$ , which lasted for about ten days. During this time he had a very persistent non-productive cough, but there was no pain in his chest. All during the fall these short attacks of fever continued. In December, 1917, the fever became more continuous, and I first saw him at that time. The striking feature on examination was an enormous number of crepitant râles over the bases of both lungs posteriorly, more especially on the right side, extending nearly up to the hilus. About Christmas, as you will see by his chart, his temperature rather suddenly rose to over  $104^{\circ}\text{F}$ , and fluctuated widely, but with a rapid defervescence during the next five days. Since that time frequent recurrences of fever have interrupted his convalescence, which has been very tedious. Whenever his temperature was even a little elevated he would cough almost incessantly, but there has been scarcely any expectoration, so that it has been impossible to get satisfactory specimens for bacteriologic study. One specimen collected on December 3, 1917, showed a pure culture of *Staphylococcus aureus*. Another, on December 10th, gave the same result. December 19, 1917, a specimen gave mostly influenza bacilli, with a few colonies of *staphylococci*. Another examination on April 8, 1918, showed mostly *staphylococci*, with a few colonies of *streptococci*. All specimens have been negative for tubercle bacilli.

Blood examinations have showed a moderate degree of secondary anemia with a slight leukocytosis. At the height of his fever the leukocytes were 13,600, with 83 per cent polymorphonuclears. They had previously numbered 7300, with 87 per cent polymorphonuclears, and subsequently showed 11,200, with 89 per cent polymorphonuclears, and still later became normal.

All during his illness it has been difficult to determine any localized signs. Over the midportion of the right lower lobe there has been a little dulness and a slight, though definite, tendency toward tubular breathing. The crepitant râles which

I have mentioned were exceedingly numerous, and at the present time, while his general condition has greatly improved, there are still a great many râles on both sides, but more especially on the right

Radiograms taken by Dr H M Imboden, at the height of his fever show a very sharply defined area of infiltration extending in a somewhat wedged shape from the hilus of the lung to the periphery. The edges are quite clearly defined and the density is quite uniform. You will notice that the heart is pulled over to the right, also on both sides there is a cloudiness over the lower portions of the lungs, together with irregularities in outline indicative of pleural thickening and adhesions.

These radiograms, made on January 14 1918, show that the shadow of infiltration is much less dense, while the other features remain about the same<sup>1</sup>. Please notice that in all of these plates the upper portions of the lungs are perfectly clear.

While it is, of course, impossible to say positively, it is my impression that this young man's illness began with his attack of so-called "grip" in 1906, which was, in reality, an inflammation of a portion of his right lung and pleura, that this focus has remained more or less active ever since and that his peritonitis and cholecystitis were secondary lesions. That the infection is not tuberculous seems to be established by the course of the disease and the radiograms.

In the first case the present attack is apparently the first, and probably marks the beginning of his pulmonary trouble. The colored boy's pulmonary lesion probably began in 1911, when he was ill with what he calls "typhoid pneumonia". He had a similar recurrence in 1913, and the present attack is evidently of the same nature as the previous ones. The third case which I have described appears to have lasted for thirteen years, with many exacerbations mostly mild, the last one having been more severe than any of the others.

You will note that they all have a number of features in common. While there have been many evidences of toxemia,

<sup>1</sup>Roentgenograms made May 14 and June 24 1918 are also shown in the text.

fever has been out of proportion to all the others. They have had little leukocytosis, the pulse has not been remarkably increased, and the nutrition has been surprisingly well maintained. In all of them the lesion has been in a lower lobe, physical ex-



Fig 20—Case III Taken December 27, 1917 Shows large dense area of infiltration in right lower lobe

amination and radiograms giving evidences of infiltration of the peribronchial tissues. Tuberculosis has very naturally been suspected in all of them, but can now be quite definitely ruled out.

Now these cases do not correspond with any text-book description with which I am familiar, yet they are not very infrequently seen, and are probably given a great variety of diagnoses



Fig 21—Case III Taken January 14 1918. Shows infiltration less dense and less extensive, especially in lower portion.

My own interest in this type of case has been stimulated by a report by James Alexander Miller in the American Journal of the Medical Sciences for December, 1917. He reported a series of 22 cases few of which were as severe or prolonged as



these, but which had the same general characteristics. He divided his cases into three groups. First, a subacute type, in which the constitutional disturbances are moderate and of short duration, but in which the physical signs persist from six weeks



Fig. 22 —Case III Taken May 14, 1918 Area of infiltration now quite mottled and outlines irregular

to four months, but end in perfect recovery. Second, a subacute type with recurrences, in which the attacks are the same as in the subacute type, but with one or more recurrences at intervals of several months or years. He notes that the phys-

ical signs appear in the same portion of the lung as in the previous attack, from which he assumes that the condition is a recurrence and not a new infection. Third, a chronic type in which the abnormal signs have remained fairly constant for a

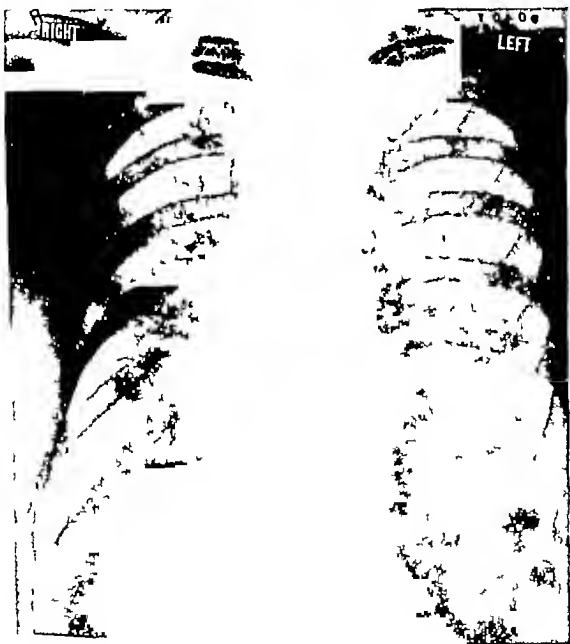


Fig 23—Case III. Taken June 24 1918. Shows appearance of diffuse irregular fibrosis of the right lower lobe

period of years. Several other American writers have also described groups of very similar cases, and they have all emphasized the decided suspicion of tuberculosis, but have been satisfied to rule it out after prolonged observation.

Pneumococci have been found in the sputum of a majority of the cases reported. Influenza bacilli are next in frequency, and various types of streptococci are occasionally mentioned.

The pathology is obscure because the disease is rarely fatal, only one necropsy having been reported. That was Hamman and Wollman's case, in which the lesion was found to be a localized bronchitis, with infiltration of the bronchial wall and foci of bronchopneumonia about the smaller bronchi. From the physical signs and the radiograms it seems fair to conclude that the lesion is always of that nature. That raises the question whether a lobar form of bronchopneumonia ever occurs. Of course, a non-tubercular bronchopneumonia usually involves all of the lobes, but that there are exceptions cannot be doubted. A localized bronchopneumonia has been experimentally produced in animals, and we have had several examples in humans coming to necropsy during the past year.

The x-ray findings are not uniform. Miller notes that 3 of his subacute cases gave normal roentgenograms, and I recall 2 cases which I have followed for several years in whom the radiograms are negative. In these the foci of inflammation are evidently very small and discrete. In others the areas are quite large, as in the ones shown you. In the hospital several times and which we eventually classified as chronic interstitial pneumonitis, as they gradually developed contraction of the chest with dislocation of the heart, and one of them has a large bronchiectatic cavity. Thus you see the lesion varies from very minutes size to large areas involving all of one lower lobe. The chronic cases with extensive pulmonary changes usually develop a purulent bronchitis which greatly impairs their health and eventually gives a picture of chronic sepsis.

When you see such cases as these you must, of course, carefully consider the possibility of a tubercular origin, and a few years ago we probably diagnosed most of them as tuberculous. They emphasize the fact, however, that a good rule to have in mind is that when physical signs are confined to the lower half of the chest, the lesion is probably not tubercular. Con-

versely, when the physical signs are confined to the upper half of the chest, the presumption is strongly in favor of tuberculosis.

The prognosis in this type of infection is very doubtful. It seems probable that the second and third cases will have recurrences and eventually develop fibrosis of the lung, with contraction and bronchiectases. The first man has a better chance than the others to overcome his infection, but I have seen none completely recover which were so severe or prolonged.

There is little to say regarding treatment, as we must chiefly rely upon fresh air, rest, and the maintenance of nutrition. I have given autogenous vaccines in several cases, but with doubtful results, though a few mild, chronic cases without extensive pulmonary changes I am sure have been benefited. During acute exacerbations some of them have a peculiar persistent, harassing, non-productive cough. This is remarkably relieved by acetanilid in 2- or 3-gram doses, repeated every fifteen minutes for four doses if necessary. Gavin, Lyall, and Morita have recently emphasized the importance of posture which favors pulmonary drainage. This treatment is undoubtedly of value in abscess of the lung and bronchiectasis, and I have no doubt it is also beneficial when there is extensive bronchitis with considerable exudation, but in most of my cases this has not been a feature, and I cannot see how postural treatment would be helpful in these patients.

*Subsequent Notes* —Case I continued to improve, though his temperature rose to 100° to 101° F every few days, and left the hospital June 13, 1918. His physical signs remained unchanged.

Case II had a moderate, irregular fever until June 6, 1918, when his temperature became normal and remained so until he was discharged on June 24th. Dulness and a few râles persisted.

Case III has also improved, but he has some fever every week or two, and his physical signs, while less extensive, are otherwise unchanged.



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## THE RELATION OF PULMONARY TUBERCULOSIS TO GENERAL PRACTICE

Consideration of Symptoms and Their Relations, Loss of Weight, Strength, and Appetite, Digestive Disorders, Dyspnea, Rapid Pulse, Fever, Pain, Cough, Hoarseness, Sputum, Night-sweats, Hemorrhage, and Menstrual Disturbances (in Women) Diagnosis, General and Differential. Treatment. Prognosis.

THE vast bulk of recent writings, as well as work, upon tuberculosis quite properly deal with highly specialized efforts to understand and control this disease. It is only by intensive concentration of effort that fundamental advances have been made in our knowledge of disease. Those of the medical profession who are devoting their lives and energies chiefly or exclusively to some specialty can only stimulate and aid progress among their co-workers by adhering closely to their ideals in work and writing, often at the sacrifice of general human considerations. It is the office of the general practitioner to co-ordinate as perfectly as possible the knowledge discovered by the specialist with that complex, sentimental, and very imperfect human being—his patient. In no other specialty is this so true as in tuberculosis, for the simple reason that it is the commonest disease of human flesh.

To the special worker, whose almost every thought and act has been devoted for years to means for defeating the tubercle bacillus, the frailties of human nature that stand in his way are intolerable. He is pursuing an ideal. To him it is unthinkable that any passing human desire or appetite should be suffered to

interfere with the absolute eradication of this universal enemy. The microscopist, the bacteriologist, and the pathologist, wrapt in the infatuation of their quest and apart from all human distractions, discover some profound truth in the life history or vulnerability of the tubercle bacillus. The special clinician, whose life's work is only a shade less consecrated to the single objective, receives the new knowledge and evolves rules for the application of this knowledge to the control and eradication of the disease. To them the chain is complete. Their facts and theories are incontestable. The goal is in sight and the way is clear, except for one consideration, a consideration which is dim or lost to the sight of the specialist, but which looms large to the general practitioner—the incalculable variations in the human family.

In general practice human beings are first children and men or women, and patients secondarily. To the specialist, especially the laboratory worker, disease and health are absolute terms, to the practitioner they are both relative.

The special clinician gives absolute rules for the control of tuberculosis. They are reasonable because they are based upon facts and have a worthy object. It is the clinician's duty and desire to urge his patient to comply with these rules. The practitioner well knows, however, that absolute compliance is impossible to obtain, and that his patient must remain his patient on through life and into the Valley of the Shadow, to the end of this tortuous and varied trail. The special clinician gives a dictum, for he speaks to disease, his enemy. The practitioner gives advice, for he speaks to humanity, his friend. Concerning tuberculosis and pregnancy, Auvard's dictum is "The young girl should not marry, the married woman should not conceive, the mother should not nurse her child." The general practitioner agrees with Auvard, but must care for the young tuberculous girl who has married, must care for the mother who has conceived, and must care for the child whom its mother has nursed.

The specialists will continue to be the producers of new knowledge to help the general practitioner in his work with tuberculous patients. They can in special institutions apply with far

accuracy their dictums, but first and last the diagnosis, treatment, and prognosis rests with the general practitioner

**Diagnosis**—Previous to discovery of the tubercle bacillus, in 1882, and to a diminishing degree for twenty years thereafter consumption (pulmonary tuberculosis) was shunned by physicians and laymen to such an extent that only after the hand of death was clearly seen upon the patient's every feature was the diagnosis pronounced. In common with other diseases in which the causative agent had been isolated, after 1882, evidence that the body had been infected by the tubercle bacillus was accepted as justifying a positive diagnosis of the disease. From a purely theoretic viewpoint, so-called scientifically, this was and still is true.

With the growth of tuberculosis sanatoria and a correct knowledge of the power of the human body, under proper conditions, to overcome tuberculous infection, there was a steady increase in efforts to establish the diagnosis as early as possible. It was, of course, obvious that the less the disease and the stronger the body, so much brighter would be the prospect of recovery once proper conditions were established. This eagerness to establish the earliest possible diagnosis (a complete reversal of the former attitude) grew to such extremes that in the first years of

a century the diagnosis of tuberculous disease was pronounced in many cases upon the flimsiest evidence and the condemned were packed off to sanatoria to be "cured." Naturally, a surprisingly high percentage of sanatorium patients were discharged "cured." So the good reputation of the sanatoria soon ran above their deservedly high value. Unfortunately, the "cured" which tuberculosis specialists applied to the ~~sanatorium~~ graduates was not accepted by the laity at its face value. In the lay mind, as in many medical minds, there still ~~lingers a remnant~~ of the old belief that "once a consumptive ~~always a consumptive~~" Many of the young people who came from the ~~sanatoria~~ in perfect health, had difficulty in re-establishing ~~themselves in~~ work and normal social intimacies ~~and~~

In a paper read before the New York ~~State~~ Medical Society January 23, 1911, I made the following ~~statement~~ "We should



enjoin more care than is now generally exercised in fixing a positive diagnosis and recommending sanatoria in legitimately doubtful cases. If we do not wish to bring upon us ultimately a well-deserved censure we must consider a negative diagnosis to be as important as a positive one." Though these words seem now quite commonplace, the discussion of my paper eight years ago left no doubt that I was moving against the current. Subsequent observation and knowledge have brought us to a realization that there is a wide difference between tuberculous infection and tuberculous disease. Probably 90 per cent or more of all human beings who reach adult life harbor tuberculous infection. Not more than 20 per cent ever have tuberculous disease. Increased experience has carried me even further than the stand I took in 1911. I now feel that in doubtful cases it is usually far worse to make an erroneous positive diagnosis of pulmonary tuberculosis than an erroneous negative one. The former can never be eradicated. The patient is branded for life, even though it is later said that his disease is "arrested" (which term is now correctly used instead of "cured"). If a negative diagnosis is erroneous, intelligent observation is almost sure to correct the error in time to accomplish all that could have been gained by an earlier diagnosis. Certainly this is the broader and more human stand to take. In this way, always on the alert, the general practitioner should lean to a negative diagnosis in doubtful cases until evidence develops which renders his position untenable.

When a diagnosis of most infectious diseases is made it either stands, or subsequent developments eliminate it by proving clearly that the symptoms were due to another disease or condition. Such is the case when a patient thought to have typhoid fever is found to have *Plasmodia malarie* in his blood and no Widal reaction nor rose spots, and when a sweat brings the temperature to normal. So may a diagnosis of gall-stone impaction prove to be appendicitis, or a diagnosis of scarlet fever may turn out to be röteln, and so on. It is not so when pulmonary tuberculosis is pronounced. Even when doubtful the diagnosis can rarely be excluded. Too often no other definite disease develops to take its place. Even though pneumonia, typhoid, or

influenza may develop or be diagnosed subsequently, who can prove that there is not tuberculosis in the lung besides? Therefore, we must be extremely cautious in pronouncing the diagnosis of pulmonary tuberculosis.

With the foregoing understanding I will proceed to the more detailed consideration of the diagnosis. The best general guide, when considering any given case, is to recall one or more individual patients whom we have been able to observe long enough to fix the significance of similar symptoms. It is upon the study and analysis of large groups of cases that we base our most impressive discussions and papers, but the physician learns and retains the most valuable knowledge for his future guidance from individual patients.

**Children.**—The extreme rarity of characteristic physical signs and the difficulty in obtaining sputum for examination in children under fourteen years of age renders a conclusive diagnosis impossible in the majority of suspected cases. Although tuberculin reactions are obtained in a smaller percentage of all persons under fourteen years than in adults, even here a positive reaction only signifies that the subject was at some time infected by tubercle bacilli. This is not the information we seek. We wish to know whether or not the patient is ill from tuberculosis, if he or she has tuberculous disease. Therefore, if its significance is wrongly estimated, a positive reaction may entail unjustifiable hardships and restriction upon the family and the patient. For the advancement of scientific knowledge it is permissible to employ the tuberculin skin tests, but not for the diagnosis of pulmonary tuberculosis. If interpreted by the clinician who has taken the history and physically examined the patient, x ray findings may rarely be of help in diagnosis. In the vast majority of these little patients, however, when the history, bacteriologic, and physical findings leave us in doubt, the x ray findings are either negative, vague, or confusing.

Cough, elevation of temperature, loss of weight, palpable cervical glands, and even râles in the lower lobes, due to acute infections, lead to many incorrect diagnoses in children. Distinct dulness on percussion with bronchial or marked bronchovesicular

breathing is rarely found in young children except over pneumonia or just above the level of an empyema. In fact, characteristic physical signs of pulmonary tuberculosis are so rare in young children that these evidences of pulmonary inflammation strongly suggest some other infection.

As stated, it is rare that tubercle bacilli can be demonstrated in pulmonary tuberculosis of children. In those who cannot be made to raise any sputum for examination, we may examine smears taken directly from the larynx. Bacilli discovered in this area, of course, clear up any doubt. But even this procedure, though it should be followed, is of help in only a very small percentage of cases.

We are, therefore, thrown almost entirely upon history and symptoms for the diagnosis in children. Family history as well as the history of other intimate associates is of importance. The parents, especially the mother, is most vital. When a child presents all other evidences strongly suspicious of pulmonary tuberculosis, if its mother is known to have had the disease when the child was born, a positive diagnosis should be made. Positive evidence of pulmonary tuberculosis in other intimates of the child is of like but less weighty importance as positive evidence. The conditions under which the child lived during such exposure should be considered. The less sanitary and the greater the degree of indoor exposure, the more likely was infection to have taken place. The known ingestion of tuberculous cows' milk could not be ignored as a possible source of the infection, but whether any considerable number of infections from cows' milk give rise to pulmonary disease has not been proved. It is at present felt that most human tuberculosis of bovine origin involves chiefly other body structures.

Those infectious diseases which involve specially the respiratory tract, such as pneumonia, measles, and influenza, are predisposing causes to the development of pulmonary tuberculosis in children as well as in adults. Though it is possible that these diseases prepare a fertile soil in the respiratory tract for implantation of tuberculous infection, it is more likely that they lower resistance and permit growth and spread of a previous latent in-

fection. No matter which is the true sequence, when symptoms and signs of pulmonary disease, with cough and temperature, continue for a month or more after the average duration of any of the acute diseases, and no other cause can be discovered, such as local or general sepsis, it is fairly safe to make a diagnosis of pulmonary tuberculosis. Diabetes mellitus, which is so commonly associated with pulmonary tuberculosis in adults, is rare in children.

The following are the commonest symptoms met with in pulmonary tuberculosis of children

Pallor, or cold extremities

Persistent evening temperature— $99\frac{1}{2}^{\circ}$  F or higher

Cough for one month or longer

Dyspnea on moderate exertion

Loss of, or failure to gain, weight.

Large palpable lymph nodes

Sweating on cool nights

Prolonged loss of appetite

Pain in chest, repeated or persistent, in the same area.

Hemoptysis, which must be carefully differentiated from nose-bleed, which may occur at night, be swallowed, and later vomited

Physical signs, especially persistent small or medium-sized moist râles in one or both upper lobes

Normal puerile breathing is so like bronchovesicular breathing of moderate infiltration of lung that the breath as well as the voice sounds are rarely of value in children. Neither is dulness on percussion likely to be detected except in very rare instances.

When three or more of the above-mentioned symptoms are present in a child who is known to have been exposed to tuberculous infection a positive diagnosis should be made. An erroneous positive diagnosis in a child does not work the same injustice that it does in adults, especially young adults.

Adults.—The great variety of gross pathologic changes in pulmonary tuberculosis and the various ways that different human organisms respond to this disease in its early stages necessarily reduce the early diagnosis of pulmonary tuberculosis to a matter of individual judgment in a large percentage of cases, even in adults. Undoubtedly a difference in the toxicity of dif-

ferent strains of bacilli adds to the protean nature of the clinical picture

The demonstration of tubercle bacilli is not always necessary to make a fairly reliable positive diagnosis, but the diagnosis remains uncertain in some cases until they have been found. Even though bacilli be discovered in the sputum early in our investigation, we should continue the classical process of diagnosis by exclusion to its completion. It is only by such means that we will avoid overlooking important complications. Graves' disease, heart disease, diabetes, nephritis, or any one of many serious diseases may be the dominant illness in a person who has pulmonary tuberculosis with bacilli in the sputum. Fortunately, the general practitioner has rarely to contend with the often biasing influence of a previous diagnosis. He works with virgin clay. The subject has usually been his patient from the beginning of symptoms and often for years before, perhaps from birth. If this gives him more freedom it also gives proportionately great responsibility. His diagnosis, right or wrong, when expressed unequivocally is very likely to stand. When the case is clear, he is almost sure to be right. When difficult, the diagnosis is apt to be a question of individual judgment, in which case a subsequent examiner, if he be a popular consultant, is not likely to disagree, first, because he could not prove his point, and second, because he would not continue to be popular. Therefore, one should lean to the negative diagnosis while providing for the patient's general health and continuing to investigate until either a positive or a negative diagnosis can be pronounced with reasonable certainty. If this cannot be done in a reasonable time, consultation may be sought at any time, but for diagnosis, where there is any room for doubt, the patient's physician will be much wiser to have his consultation before he expresses his opinion. Almost every symptom and physical sign known to medicine may be present in pulmonary tuberculosis. Yet any of them may be produced by other diseases.

There are two distinct types of clinical history of pulmonary tuberculosis. (1) The gradual or sudden appearance of symptoms or signs without preceding illness from other cause. (2) A failure

properly recover from some other illness or injury, with the development of symptoms or signs suggestive of pulmonary tuberculosis

Although pulmonary tuberculosis may exist to a varying extent without producing any symptoms or signs, the following symptoms are the most common, and two or more of them are present in nearly every case

- Loss of weight
- Loss of strength
- Loss of appetite
- Digestive disorders
- Dyspnea.
- Rapid pulse
- Fever
- Pain
- Cough
- Hoarseness
- Sputum
- Night sweats
- Hemorrhage
- Menstrual disturbances (in women)

*Loss of weight*, from any cause, may signify lowered resistance, which permits the development of pulmonary tuberculosis in one whose focus of infection would otherwise have remained latent. On the other hand, loss of weight may be a symptom and result of active tuberculous disease. Therefore, the loss of 5 per cent or more of the individual's normal weight should be considered suggestive of pulmonary tuberculosis when another likely cause cannot be elicited. It is only suggestive and of no value in the absence of other symptoms

*Loss of strength*, though more difficult to measure, occupies in the symptomatology of pulmonary tuberculosis a position similar to that of loss of weight. It may be either the cause or a result. Its value in diagnosis depends upon its relation to other manifestations or findings

*Loss of appetite*, although more or less similar to the two foregoing symptoms in significance, appears to have a more consistent

relation to the disease in some cases. Especially does this apply to the appetite for breakfast. In some cases the first symptom complained of is either a loss of appetite or distinct aversion to food in the early morning. Though this symptom should be viewed with peculiar suspicion and pulmonary tuberculosis be always looked for in these patients, we must not lose sight of the fact that modern habits of life have developed this early morning aversion to food in a large percentage of otherwise normal people. Early morning nausea, so common in chronic gastritis from any cause, must not be mistaken for a symptom of pulmonary tuberculosis.

*Digestive Disorders* — Besides loss of appetite for, or aversion to, breakfast, indigestion, pain, or discomfort after taking food and other evidences of disturbance of digestion are commonly experienced early or throughout the course of pulmonary tuberculosis. Hyperacidity, with its epigastric pain or discomfort, which is felt most frequently when stomach digestion should be almost complete, may be the first manifestation of pulmonary tuberculosis. Sour, acid, or bitter eructations, with or without gastric and intestinal flatulence, are common in these cases. Any cough or scanty sputum is usually ascribed to the "stomach" by these patients. Late in many cases of pulmonary tuberculosis the most distressing and uncontrollable symptoms are due to disorders of the stomach and intestines.

*Dyspnea* — Early in the course of pulmonary tuberculosis it is difficult for many patients to know whether they experience shortness of breath or loss of endurance. They may tire more easily than they did formerly, but do they actually feel short of breath? Dyspnea, or lack of oxygen supply to the system, no doubt is a large factor in the production of tired feeling or lassitude. The individual's acuity of self-analysis determines which one he will complain of. Furthermore, people who habitually move slowly and with deliberation are not likely to recognize or experience dyspnea. Those who have been accustomed to move about quickly more quickly recognize shortness of breath, and mention it as such. No doubt dyspnea is usually in direct proportion to the extent of lung compromised by disease. Yet this is not always the case,

as proved even by autopsy. So far as physical signs of pulmonary change indicate, there is very often dyspnea far in excess of the lung involvement. This is strikingly illustrated in acute general military tuberculosis.

It should be remembered that profound anemia from any cause is associated with dyspnea upon slight provocation, even without any muscular exertion. Dyspnea due to cardiac disease will not be mistaken for a symptom of tuberculosis if examination of this organ is part of the physician's routine, as it should always be. Before excluding the heart as a cause of dyspnea, one should always consider the possibility of myocardial as well as valvular changes.

*Rapid pulse* is of corroborative importance in the diagnosis of pulmonary tuberculosis only when associated with other significant symptoms and signs. An adult with a pulse-rate of 95 per minute or more, when at rest on several occasions, in the absence of other known cause, should be examined for evidences of tuberculosis. Rapid pulse, of 110 per minute or more when at rest, is of more prognostic than diagnostic value. In such a case recovery from pulmonary tuberculosis is less likely than in those with a pulse-rate less than 95 per minute. One must keep in mind the ease with which the pulse of many people is markedly accelerated by merely the nervousness due to the ordeal of examination. In fact, this renders the pulse-rate of little value when only one examination is performed. The characteristically rapid pulse of Graves' disease is probably the most prominent example of rapid pulse due to disease which might be attributed to pulmonary tuberculosis. On several occasions while examining patients who had been diagnosed as having pulmonary tuberculosis and referred to me for admission to the Otisville Sanatorium I encountered cases of Graves' disease, with rapid pulse, slight cough, moderate tremor, and slight enlargement of the thyroid gland. Further investigation excluded pulmonary tuberculosis. They were uncomplicated cases of Graves' disease. One must not be deceived by the characteristic sweating experienced by those who have Graves' disease. I have also seen several cases of Graves' disease complicated by pulmonary tuberculosis.



*Fever* —Although there is no infallible rule in clinical diagnosis, if a patient should have a body temperature of  $99.6^{\circ}$  F or more every evening and  $98^{\circ}$  F or less every morning for ten days or longer, and sepsis can be excluded, a diagnosis of tuberculous disease is fairly safe. In which case it only remains to locate the site of the disease. Clinical experience has developed the fact that in the temperate zone typhoid fever, septicemia, and tuberculosis are the only diseases which produce a continued fever for more than three weeks. So, if two of these can be excluded, the remaining one is the correct diagnosis. The paratyphoids are included under the term "typhoid" in this group, although they usually run a course of less than three weeks. A constantly subnormal temperature in the early morning is about as significant of tuberculosis as is the evening fever. Yet there are some cases of tuberculosis in which the temperature remains above normal throughout the entire twenty-four hours for many days. On the other hand, in some cases early morning subnormality is the only variation of temperature observed. This latter may occur in cases of very slight involvement with extreme general depletion, or with advanced wide-spread lesions walled off by fibroid or calcareous deposit, where the combative elements of the body are too deficient to react to the toxic substances of the disease. In some of these old cases the protective wall may be too dense to permit the toxic substances to reach the blood and produce a temperature reaction. In all of these cases the body vitality is very low and we usually obtain no reaction (negative) to tuberculin and complement fixation tests. In the advanced cases, of course, the diagnosis is usually readily made by other signs and symptoms, irrespective of the temperature.

In all cases where the diagnosis is difficult the temperature should be taken twice a day (7 to 8 A. M. and 4 to 6 P. M.) every day for seven consecutive days. The thermometer should be held under the tongue, lips closed, for three to five minutes when a rectal temperature is not taken. Although fever is a symptom of all infectious diseases, and extreme muscular exertion as well as emotional excitement may cause elevation of temperature, it is the consistent daily variation, elevated in the evening and sub-

normal in the morning for some time, which is more or less characteristic of tuberculosis. Yet there are some cases of pulmonary tuberculosis with very erratic variations of body temperature, and a smaller number in which the temperature is always normal or very nearly normal.

*Pain*—Crile has said that the reason visceral lesions are frequently not associated with pain is that they do not set up any muscular protective action. The earlier theory was that sensory nerves are not distributed to those viscera in which lesions cause no pain. Whatever the reason, it is a fact that pain in the chest does not occur in pulmonary tuberculosis until the pleura is invaded by the lesion or by the inflammatory zone surrounding the lesion. Some lesions begin their clinical history with involvement of the pleura, in which case pain is an early symptom. Pleurisy, with or without the prompt production of fluid effusion, may be the first manifestation of pulmonary tuberculosis. If, as is most often the case, the mural pleura is involved, the pain is likely to be felt in the region of the nipple, along the margin of the scapular or over the apex of the lung. In rare instances pain is felt in other parts of the chest. When the diaphragmatic pleura is the site of the lesion, pain may be reflected to and felt in the abdomen or neck. If the central part of the diaphragm is involved, the pain is felt in the neck along the border of the trapezius muscle. Lesions near the outer margins of the diaphragm reflect pain to different parts of the abdomen. In this way is explained some peculiar errors of diagnosis recorded in the literature. Diagnosis of peritonitis, appendicitis, gall-stone impaction, gastro-duodenitis, ulcer of the stomach or duodenum, absence of the liver, subdiaphragmatic abscess, pancreatitis, portal thrombosis, intestinal obstruction, renal colic, and diaphragmatic hernia are some of the diagnoses which have been made in cases of diaphragmatic pleurisy. On the other hand, many of these conditions have been called pleurisy because they not infrequently reflect pain to the lower chest. It is also quite common in disturbances of the liver and gall tract for the patient to feel pain in the right shoulder. These facts merely emphasize the importance of always approaching a diagnosis by comprehensive exclusion.

Lieutenant Walter L Rathbun has called my attention to a procedure for the differential diagnosis of diaphragmatic pleurisy from intra-abdominal conditions, such as biliary or kidney stone and appendicitis, when the former is associated with pain and tenderness on pressure in abdominal regions. It seems this procedure was recently first applied in the Naval Hospital at Newport. It has been tried in only half a dozen cases, but has given consistent results in every case. The procedure is to palpate the site of abdominal pain and tenderness while the patient holds his breath. If it is due to diaphragmatic pleurisy, both pain and tenderness are absent while the patient holds his breath. The theory of reflected pain would place this observation upon a rational basis. It is certainly worth further trial and seems to promise valuable aid of the difficult cases, which have led to unnecessary laparotomy.

In central tuberculous lesions there may be no pain in the chest, even though large cavities develop. Pain, in the form of neuralgia, due to circulating toxins, either specific—from the tubercle bacillus—or from gastro-intestinal ferments, is present in some cases. These neuralgias may involve any of the sensory nerves. Intercostal neuralgia of this origin is often mistaken for pleurisy. Pleuritic pain is likely to be produced or increased by deep breathing, cough, laughing, crying, or sneezing. It is usually markedly relieved by steady compression of the affected side of the chest between the two open hands. Not so with intercostal neuralgia, which is greatly accentuated by pressure over the points where the lateral and posterior cutaneous branches of the involved nerve or nerves pierce the deep fascia. This toxic neuralgia of the cutaneous abdominal nerves might be mistaken for acute disease of abdominal viscera unless the possibility is thought of and an error avoided by proper palpation as well as consideration of other symptoms. Neuralgia of the head, face, or extremities is more likely to occur late in pulmonary tuberculosis, when the diagnosis is obvious.

In a considerable percentage of those in whom the diagnosis is relatively difficult there is a feeling of dull ache, the ache of over-tired muscles in one shoulder, or along the margin of the scapula.

It is an open question whether this feeling is due to pleurisy or muscle exhaustion, so it should not be given too much weight in diagnosis.

Dryness, rawness, or pain in the larynx or throat when swallowing, especially when swallowing fluids, if persistent, should be viewed with suspicion. A laryngoscopic examination is indicated in these cases. The pain of acute lobar pneumonia is usually associated with symptoms and history which prevent error. The same may be said of angina pectoris. The pain of aneurysm and solid intrathoracic tumors is more likely to make the examiner think of pulmonary tuberculosis, but a careful analysis of history, symptoms, and physical signs, especially the latter, will prevent error. Here the x-ray is often of real value in diagnosis.

*Cough*—Because cough is the commonest symptom of pulmonary tuberculosis, it has been the commonest cause of mistaken diagnosis of this disease. Cough is not only a symptom of disease, it is also, like sneezing, a normal involuntary protective measure. It may be availed of voluntarily, but it is always a protective act. It is peculiar inasmuch as it is one of the very few symptoms of disease that cannot be hidden from one's associates. Next to pain, cough is probably the most common symptom in the category. Next to pain, it also has the most varied significance. Yet, cough is a prominent symptom in such a large percentage of all cases of pulmonary tuberculosis that it creates lay suspicion as soon as heard. There is a tendency on the part of many to attribute only certain kinds of cough to consumptive origin. "Hollow," "racking," and "laryngeal" have dreadful significance to the phthisiophobic. A special type of cough is characteristic of consumption early and even in the late stages of some cases may be only an almost noiseless clearing of the throat, very susceptible to voluntary control or suggestion. In such cases, even where there is considerable sputum, This is particularly noticeable in a well-to-do class of patients. I have often made rounds at the Sanatorium, where there are nearly 600 cases.

culosis, and not heard a single cough in the three hours of my rounds

If a patient has had a cough continuously for six weeks or longer, and we are unable to discover another cause, it is highly suggestive of tuberculosis. The uvula, if elongated, may produce cough until it is amputated. Posterior nasal drippings or other pharyngeal irritations may be the cause. Hypostatic congestion of the larynx or bronchi must also be excluded. Cough due to acute infections or neurasthenia rarely lasts six weeks. Cough should never be considered as confirmative evidence of the presence of pulmonary tuberculosis, it is only suggestive of the possibility of the presence of this disease.

*Hoarseness*, when persistent, especially if associated with pain on swallowing, is sufficiently suggestive of tuberculous laryngitis to demand thorough investigation. In the absence of other and confirmatory evidence I never like to accept as final the opinion of a laryngologist who is highly specialized in tuberculosis in these cases. I find that they are inclined to attribute every partially immobilized and reddened cartilage or false cord and neighboring structure to tuberculosis. In this I do not agree with them. Many of these cases clear up in time and in such a way as to exclude the probability of tuberculosis.

*Sputum*, like cough, is never characteristic of pulmonary tuberculosis. There are two substances which may be found in sputum—one almost, the other quite, indicative of this disease—blood and tubercle bacilli. Nearly all persons with pulmonary tuberculosis, except those in which the lesion remains confined to the pleura, raise or have at some time raised sputum. Never is the gross character nor the amount diagnostic. A curious belief has been held by some that if sputum sinks in water, it is due to consumption, if it floats, it is not. This is, of course, mere superstition. If sputum is filled with air-bubbles it will float. If it is relatively solid it will sink, irrespective of the disease. Sputum, even from well down in the lung, may be raised without cough, especially early in the morning. When sputum of any character is raised for a month or more it should be examined bacteriologically. Large quantities of sputum, a teacupful or more in

twenty four hours, is suggestive of bronchiectasis or large ulcerative cavity. Extremely fetid sputum is strongly suggestive of lung abscess. Slightly fetid sputum in large amount for a long time suggests bronchiectasis.

*Night-sweats* —The laity and many of the medical profession consider this symptom as almost positive indication of consumption. Night sweats frequently occur in pulmonary tuberculosis, and are usually of serious significance. They are likely to occur only in those cases where the diagnosis is otherwise not difficult. In fact, when night-sweats occur in a person who does not present the more or less characteristic temperature variations, cough, dyspnea, pains, sputum, hemorrhage, bacilli, or physical signs, the sweats are almost certainly not due to pulmonary tuberculosis.

General depletion, from prolonged anxiety, overwork, excesses (alcoholic or sexual), or digestive disturbance not infrequently produces nocturnal drenching or local perspirations during sleep.

The sweats of septic infection are likely to occur irregularly throughout the twenty four hours. Malarial sweats bear a fixed relation to chills and fever. With the fall of all fevers, such as that of tonsillitis or grip, especially when antipyretic drugs have been administered, profuse sweating occurs.

Although some cases of tuberculosis have sweating confined to the neck and shoulders, many of these local sweats are of purely neurotic origin.

*Hemorrhage* (hemoptysis) needs no further emphasis to establish its place as the premier symptom of pulmonary tuberculosis. It is probably much more important at this time to give prominence to the fact that blood spit from the mouth is not a sure sign of this disease. Next to the presence of tubercle bacilli in the sputum and confirmatory physical signs in the chest, hemoptysis is the most positive evidence of pulmonary tuberculosis when some other source of the bleeding cannot be demonstrated. Yet, the rare appearance of minute particles of blood in the sputum, even though a point of bleeding cannot be seen in the mouth, throat, or nose, is not enough upon which to base a positive diagnosis of pulmonary tuberculosis. Bleeding from a gastric ulcer or from

difficult to differentiate from true hemoptysis. The patient's ability to tell whether it was vomited or raised from the lung is not always accurate. In these cases, when physical examination cannot fix the site of the lesion, there is an extreme waxy pallor following hemorrhage from a gastric ulcer, which is almost never so marked after an initial pulmonary hemorrhage. Yet, I have seen several instances where a confusion of the two conditions by experienced examiners was subsequently proved.

Before pronouncing a positive diagnosis solely upon hemoptysis, even when a teaspoonful or more of blood is raised, we should consider esophageal or laryngeal varicosities, cardiac disease, or aneurysm. Injury which does not penetrate the chest wall is not likely to cause pulmonary hemorrhage unless it be extremely severe. Some chemical vapors, such as the poison gases which recently emanated—quite appropriately—from Germany, produce bleeding from the lungs. A knowledge of the industry in which the patient is engaged prevents error of diagnosis.

*Menstrual disturbances*, such as prolonged intervals between the flow, scanty or suppressed menstruation, are rather common in women or girls who have pulmonary tuberculosis. For this reason pregnancy is frequently overlooked in these patients. It is difficult to believe that the reverse could occur, that an erroneous diagnosis of tuberculosis would be based upon disturbed menstruation.

**Physical Signs.**—Probably the most difficult rôle to fill in the examination of one suspected of having pulmonary tuberculosis is that of an honest interpreter of the physical findings. It is my impression that, as a general rule, the average well-versed general practitioner is the physician who most often fills this rôle. His special senses are just as acute, but he is not under the urgent demand for exact knowledge that faces the specialist. There are a number of cases in which positive diagnosis can be firmly established, where focalizing physical signs are vague, scanty, or absent. In this situation the specialist at times imposes upon credulity without imposing injustice upon the patient. In those cases where the diagnosis is otherwise doubtful—the patient's

physician, who is under no obligation to believe that physical signs are present which his special senses cannot detect, must challenge any positive findings of a specialist, if they cannot be demonstrated to his entire satisfaction. There is not such urgency in these cases to demand prompt compliance without conviction. The specialist is quite capable of honest error and should not take offense when the patient's own physician (whose special senses are sound) is honestly unable to detect signs which the specialist believes are present. Time, with intelligent investigation, will usually decide the diagnosis. As has been often said, failure to find lesions that exist is usually due to failure to look for them. It is true that the unwilling are blind, but a patient's physician is as willing as sincerity permits. If all his faculties are sound he will see, feel, or hear any phenomenon detected by the specialist, once his attention is directed to it. If, under these circumstances, he cannot detect it, sanity demands incredulity.

*Inspection*, although to be applied first in the proper sequence of the four primary methods of physical exploration, is continued intelligently throughout every examination by the competent physician. It is not only the oldest method employed, it still ranks high in importance. Naturally, the growth of complexity in the application and interpretations of other more mathematically measurable measures has deprived inspection of its former prominence. Even today, however, the wise diagnostician gives much attention and heed to his eyes. "Seeing is knowing" is not a baseless platitude in medicine any more than in other physical problems, and the more a physician intelligently looks for, the more visible indications of disease he will see.

The bearing, carriage, and voice are a fair indication of the general vigor. The furtive eyes, with pin point pupils, of a morphin habitué may keep one from attributing emaciation, dyspnea, and abnormal respiratory sounds to tuberculosis. Yet, many of these people develop pulmonary tuberculosis.

Slight goiter, exophthalmos, and tremor not infrequently establish a diagnosis at the first glance. The bronzing of Addison's disease is likely to be overlooked by indifferent inspection. Many



other visible indications of various diseases could be named. It is only necessary for the physician to keep his faculty of inspection trained and always on the alert.

The characteristic physical picture of the advanced consumptive needs no detailed description. When a thin, pale face, with marked zygomatic prominences capped with a patch of high color, deep-set steady eyes and a small neck, speaks with a high pitched voice of little volume, further investigation rarely changes the first impression.

The dusky or cyanosed lips and extremities, as well as other evidences of dyspnea, and clubbed fingers may be due to cardiac as well as pulmonary disease.

*The Chest* — Perhaps the most commonly neglected essential in physical examination of the chest is free and unrestricted access to the parts. This is naturally an error which is most often committed in the examination of women and girls. I think it is safe to say that half of the undiagnosed cases of pulmonary tuberculosis in these patients are undiscovered through unjustifiable timidity which prevents the removal of corsets and other clothing. The chest must be viewed carefully as a whole. It is by comparing the two sides that we detect asymmetry, for there is no fixed form of chest that can be called normal. Normal is a variable quality in chests as in other anatomic parts. Rickets and spinal curvature, intrathoracic growths, heart disease, past injuries, and surgical operations all produce asymmetry and deformity in the chest. Also subdiaphragmatic tumors, when large. We must exclude these causes except in those cases where tuberculosis exists with one of these conditions.

Visible cardiac action in the third left intercostal space may be due to either heart disease or tuberculosis of the left upper lobe. Localized retraction of the chest, especially of one or both supraclavicular fossæ, is usually due to localized destruction of lung tissue. However, bad posture or emaciation from other causes may be deceptive. Limited or absent expansion over these areas is usually noted in tuberculosis. Injury or tumor of the spinal cord at the level of the fifth cervical vertebra causes entire loss of costal breathing. The entire chest is as immobile as marble,

with only abdominal breathing, in the form of paraplegia. The "ala," "flat," "narrow," and many other special forms of chest have been called characteristic of pulmonary tuberculosis, but they are only characteristic in those cases where abundance of other evidence is available.

*Palpation*, besides confirming deformities and peculiarities of expansion noted by inspection, measures vocal fremitus and detects enlarged lymph nodes, which are present in the neck, axillæ, or groins in many cases of tuberculosis. Hodgkin's disease, lymphadenoma, enlarged cervical glands due to throat infections, and syphilitic adenitis must be excluded.

Vocal fremitus is of little positive value unless markedly increased, decidedly diminished, or absent. Slight changes are of no actual value. The normal variations for different chest regions must be kept in mind to avoid incorrect interpretations. Consolidation sufficient to cause marked increase of vocal fremitus is easily confirmed by auscultation. It is only increased by consolidation of lung with open bronchi. Both percussion and auscultation are necessary to interpret the significance of absence of vocal fremitus. Vocal fremitus may be absent over hydrothorax, pneumothorax, or large solid tumors. The percussion and auscultatory sounds vary greatly in these conditions.

*Percussion*, next to auscultation, gives us the most positive evidence in all advanced pulmonary changes. In some conditions, especially fluid accumulation, it gives more valuable information than any other method short of exploration with a cannula or needle. This is largely due to the sense of resistance felt in percussion over fluid. In the early stages of pulmonary tuberculosis, where infiltration is slight or scattered, and there is slight or no pleural thickening or fluid, percussion is of little or no value. Even in many advanced cases, cavity formation, emphysema, pleural changes, and areas of consolidation are so intricately associated percussion often gives no aid. In fact, when percussion yields definite variations from the normal the diagnosis is usually obvious.

*Auscultation* is, unquestionably, the method of physical exploration, in sputum negative patients, upon which suspicions

gained by other methods must stand or fall in nearly every case. It is usually by this means that we first discover signs upon which we rest a positive diagnosis. Where the symptoms have given rise to a suspicion of pulmonary tuberculosis, it is a wise procedure to always begin auscultation of the chest with examination of the heart. In this way one obviates the rather common error of attributing pulmonary signs, due to circulatory impairment, to disease of the lung. It is not uncommon for examination of the heart to be entirely forgotten once the examiner's

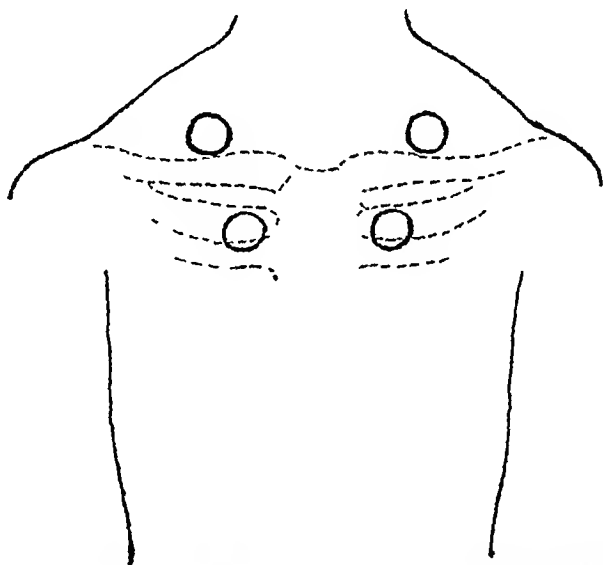


Fig. 24 — Cardinal points for auscultation, anterior surface, in the diagnosis of pulmonary tuberculosis

interest is directed to the lung. It is, of course, necessary for the examiner not only to be familiar with, but to keep in mind, the relations of underlying anatomic structure, and the characteristics of normal auscultatory sounds peculiar to different regions on the two sides.

Although the stethoscope or the listening ear (if stethoscope is not at hand) should be applied to all parts of the surface of the chest, there are five cardinal points on each side. It is extremely rare to hear signs of pulmonary tuberculosis in a chest

when none can be detected at either of these points. As indicated in Figs. 24-27, there are two on the anterior surface, two on the posterior surface, and one lateral, in the axilla on each side.

The anterior cardinal points are just above the clavicle, and near the anterior extremity of the superior border of the second rib.

The posterior cardinal points are just above the spine of the scapular,  $2\frac{1}{2}$  to 3 inches from the median line, and 1 inch from and

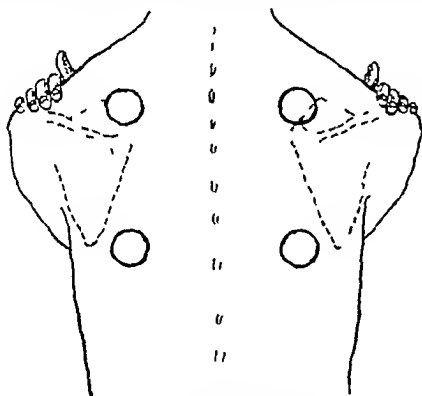


Fig. 25.—Cardinal points for auscultation, posterior surface, in the diagnosis of pulmonary tuberculosis.

to the inner side of the inferior angle of the scapula, while the patient's hand rests on the opposite shoulder.

The lateral cardinal point is high in the axilla close to the anterior axillary fold.

Much more attention is given by writers and lecturers to the pitch, duration, and intensity of auscultatory (as well as percussion) sounds in physical diagnosis than it is possible for the average medical ear to apply. Theoretically and for training the student this is both attractive and valuable. Actually the significance of a sound in physical diagnosis is nearly always known

by its quality. A subelement of quality, the distinctness with which a sound is heard, is often an aid in determining the significance. Appreciating the foregoing and with a fair knowledge of the normal and pathologic conditions that are both likely and possible, experience and good judgment will determine the degree of one's success in diagnosis.

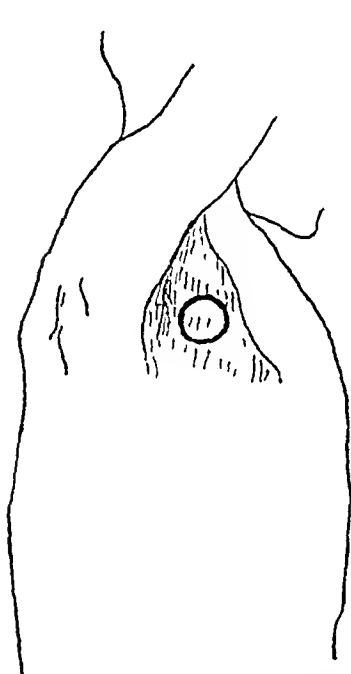


Fig 26—Cardinal point for auscultation, lateral surface, in the diagnosis of pulmonary tuberculosis, right side

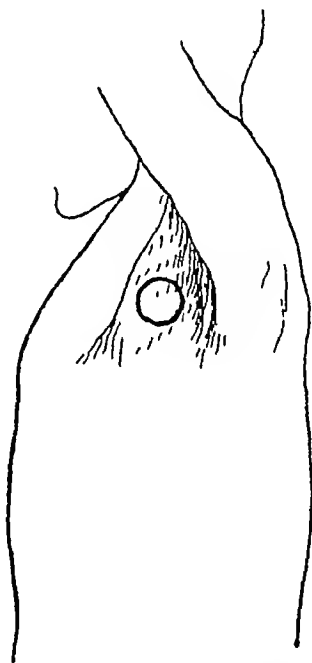


Fig 27—Cardinal point for auscultation, lateral surface, in the diagnosis of pulmonary tuberculosis, left side

I do not feel that there is any occasion here to repeat the theories and familiar facts concerning the origin of such sounds as bronchovesicular and bronchial breathing, increased vocal resonance and bronchophony, egophony, and amphoric voice and breath sounds. With the exception of bronchovesicular breathing and increased vocal resonance they only occur late in pulmonary tuberculosis.

We must first understand that pulmonary tuberculosis may exist, sometimes fairly extensive, without altering appreciably the normal chest sounds. In some cases the only change is diminished intensity of the breath and voice sounds over the involvement.

In the majority of early cases, where diagnosis by physical signs is possible, but not grossly obvious, the only signs appreciable are an increase in the bronchial quality of the breath sounds, with lazy prolongation, most noticeable in the expiratory act, bronchovesicular breathing (also called "harsh," "granular," and by many other names) and a few moist râles, which may be heard constantly or only after several acts of coughing. In most of these cases an increase in vocal resonance is not appreciable, although, theoretically, it should be present. As is well known, such signs heard symmetrically on both sides are suggestive of some other infection, such as influenza or hypostatic congestion from heart or renal disease. Tuberculous lesions are nearly always either unilateral, early in the disease, or asymmetrically placed on both sides. I am rarely willing to base a diagnosis upon bronchovesicular breathing when râles are not associated with it.

When listening to the chest during and after cough one should be on his guard to avoid misinterpretation of râle-like sounds produced in the muscles or the esophagus.

*x Ray*—Except in those cases where the patient or his friends request an *x-ray* examination it is probably best to arrive at a decision without employing this agency. When the interpretations are made by a specialist who has not examined the patient confusion of opinion is very likely. In institutions, where autopsies may be performed upon those who die, *x ray* examinations should be made, for it is only in this way that we may come to know the real value of this agency in the diagnosis of pulmonary tuberculosis. Also in those patients where symptoms or signs suggest the possibility of intrathoracic tumor or aneurysm. For determination of the extent and character of lesion and cardiac displacement, where the diagnosis is established, *x ray* is of value.

*Tuberculin*—The von Pirquet and Moro skin tests are harmless, but of little aid in the diagnosis of tuberculous disease.

Positive reactions only prove the presence of tuberculous infection and a negative reaction does not exclude it. They are of no aid in the diagnosis of pulmonary tuberculosis. The Calmette eye test has no advantage over the skin tests, and is injurious to the eye in some cases. The subcutaneous injection of a fraction of a milligram up to 10 milligrams of old tuberculin (like repeated doses of potassium iodid to produce râles, or bacilli in the sputum, where none were present) is, in my opinion, inexcusable.

After extensive and painstaking investigation with tuberculin at the Otisville Sanatorium I am convinced that, in the present state of its development, it should be confined to the field of experimental medicine.

*Complement Fixation*.—This test is admittedly still confined to the experimental stage.

*Treatment*.—It is fairly well known by now that in pulmonary tuberculosis treatment should be confined to the individual, for there is no known treatment of the disease which is of proved value. It is inevitable that in a disease which so often improves under very contradictory conditions, a great number of specific substances and measures should gain a reputation for benefiting or curing it. Air, food, and rest are essentials which are too well understood to call for discussion.

There are in many cases of pulmonary tuberculosis symptoms which must be relieved or diminished in severity. There are three major means at the disposal of the physician for relief of these symptoms which should be employed in the order named.

1 *The Patient's Mental Attitude and Will Power*.—The patient must be freed from any idea that the disease is to be certainly progressive and hopeless. He or she must know that they can, by proper acquiescence and shaping of their mode of life, almost certainly conquer the disease, living usefully and happily, as thousands have done. The will power can often control in jurious cough.

2 *Physical Measures*.—Absolute rest in bed in good air will often control pain, cough, temperature, rapid pulse, and many other annoying symptoms. Strapping the chest often relieves the pain of pleurisy. A proper balance of rest, exercise, and open

air and diet usually restore the appetite for wholesome and attractive food Stomachic tonics rarely do

3 *Drugs*—Only when no other available means will control symptoms should drugs be employed When prescribed, they are, of course, given just as they are for similar symptoms in other diseases

The *sanatorium* falls under the head of physical measures, although a properly conducted sanatorium embraces all three measures in their proper relation to each other It is here that the maximum of good open air is obtainable No doubt, if it were possible to treat every case of pulmonary tuberculosis in a good sanatorium and keep the patient's mental attitude as is desired throughout, this would give the best physical results But, owing to the varied circumstances and personalities of those affected, this is quite impossible. In a large percentage of patients of moderate circumstances the sanatorium should be looked upon as an institution of learning and training for the new life they must lead After this, by consultations, which diminish in frequency as the healing and recovery is established, their home physician acts as watchman

The very poor, who cannot live properly for lack of money, and the erratic or unreliable should certainly go to sanatoriums

Those in good circumstances of proper mental attitude who can be depended upon to follow advice often do very well and the disease becomes arrested without sanatorium training

Some specialists are uncompromising in insisting upon sanatorium treatment in every case as soon as a positive diagnosis is pronounced Others advise treating all cases in their homes, while permitting all who are able to be up and about to continue at their regular work.

Here, as in nearly every other situation, the proper attitude lies midway between the two extremes of advice To repeat, each case must be advised and treated individually Knowing what we wish to accomplish, we must consider carefully the material (meaning the patient) and the measures which are best adapted to each case Under no circumstances should the patient's mental attitude be ignored It is of great importance in shaping



the result Here ripe experience and very broad good judgment are essential in the physician

Probably one of the most potent factors in the control of tuberculosis, pulmonary as well as other varieties, is the removal of infected or exposed children from injurious home conditions. Even though such removals may be only for a few months or years, it often results in the establishment of healthy resistance which prevents the development of the disease. The practitioner should be always on the alert to see that these little ones are thus protected. It may be accomplished by improved living conditions in a preventarium or in a sanatorium. Each case must decide which method should be employed.

Finally, the practitioner should never fail to report every positive diagnosis to the health authorities of his city or district.

**Prognosis.**—As there is need of good judgment in the diagnosis and treatment of pulmonary tuberculosis, so there is need of limitless tact and diplomacy in prognosis. Previous to twenty five or thirty years ago, when a positive diagnosis was rare before the disease had reached what we now call the advanced stage, nearly all died in from one to three years, the average being about two years. At that time the general custom of keeping all fresh air from the patient contributed to life's brevity. Now it is not rare to see advanced cases of the disease live from three to five years or longer. Probably the average duration of life after a diagnosis of pulmonary tuberculosis is pronounced is now somewhere between five and ten years. Some will die a few months after a diagnosis is first possible, while others, in no measurable way different, will develop the chronic fibroid type of lesions and live fifteen or twenty years. The factors which determine the issue are so numerous, and many so impossible to measure, that one can rarely predict with even approximate accuracy how long any individual patient will live.

The life duration of ancestors, the personal mental attitude, the general virulence of the culture which infects the patient, its peculiar virulence to this particular individual, and his or her resistance or lack of resistance, the site of the lesion—chance mixed infections—the patient's conduct, accidental exposures,

and many other factors, some known, but more incalculable, interdict prophecy. Even when a patient's lungs appear to be riddled with large and small cavities and dyspnea is so marked that they cannot sit up in bed, when they are wasted to a mere skeleton and the pulse is rapid and thready, and one week more of life seems beyond the realm of possibility, slight improvement may ensue, giving the sufferer just strength enough to drag his mortal agony on through months of voiceless pain.

I will not repeat the well known symptoms that usually indicate a short and unfavorable course. Every text book on medicine recites them.

For obvious reasons, it is never wise to dim the optimistic attitude of those who are so blessed. So long as it is not permitted to interfere with proper conduct of the case, for treatment and the prevention of spread of the disease, a cheerful attitude and belief in recovery must be held out as long as possible.



## CLINIC OF DR E LIBMAN

### MOUNT SINAI HOSPITAL

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#### THE CLINICAL FEATURES OF SUBACUTE STREPTOCOCCUS (AND INFLUENZAL) ENDOCARDITIS IN THE BACTERIAL STAGE<sup>1</sup>

DURING the last few months you have had demonstrated to you a number of cases of subacute endocarditis, and today I shall summarize the symptoms of the disease in the active stage

You know now that the cases of infection of the valves of the heart that run a subacute course have certain features that make the clinical picture quite distinctive. You also know that the disease in over 95 per cent. of the cases is due to an anhemolytic streptococcus, the so-called *Streptococcus mitis*, and that in most of the remaining cases the influenza bacillus is present. The clinical picture of the cases due to the influenza bacillus is practically the same as that found in the streptococcus cases, with the exception that marked clinical evidence of renal disease is more common in the former type. So that whatever I say concerning the symptomatology of the streptococcus cases will hold true for the influenzal cases.

The first author to draw prominent attention to the disease was Sir William Osler. He already referred to the condition in 1885 in the Gulstonian lectures. In this publication will be found reference to earlier observations of Wilks, Bristowe, and Coupland. Following a later paper by Osler there appeared an important contribution in England by Horder. The most important German studies are those of Lenhartz and Schotmueller, both of whom entirely ignored all earlier authors.

<sup>1</sup> Based on demonstrations of cases in the wards of Mount Sinai Hospital in March, 1918, and on part of a presentation to the Johns Hopkins Medical Society in March, 1917.

in foreign countries. The disease had been known to Fraentzel, Litten, and von Leyden. Latour in 1912 published a monograph from which it is evident that the disease was known to French authors (Lancereaux in particular) for a very long time, the observations of Rapin dating back as far as 1871. Rapin described in some detail the tender cutaneous nodule of the disease. The views of Harbitz, of Christiania, on the pathology of various forms of endocarditis constitute a remarkable contribution to the subject. This author was quite early convinced of the possibility of spontaneous healing processes occurring in the lesions of the disease. In this country, as you are aware, very important studies have been made by Rosenow, these being mainly of a bacteriologic and immunologic nature. There are valuable contributions by Billings, Major, and others.

The disease has been given many names: chronic septic endocarditis, chronic ulcerative endocarditis, chronic infectious endocarditis, septic rheumatic endocarditis, endocarditis lenta, endocardite maligne a forme subaigue, etc., but the name by which it has been mainly known is "chronic malignant endocarditis." Until the virus of rheumatism is definitely proved to be of the nature of bacteria the term "subacute bacterial endocarditis" is a useful one, as it includes all the cases running a subacute course and of bacterial origin.

The frequency of the disease has been much underestimated. While not as common as rheumatic or syphilitic endocarditis, it is much more frequent than bacterial cases running an acute course (so-called "acute malignant endocarditis"). This holds especially true if one rules out cases of terminal bacterial endocarditis. Up to March, 1917, I had notes of 182 cases, 144 in the bacterial stage and 37 in the bacteria-free stage, and one case that had become bacteria free under observation. I have witnessed at least 65 postmortem examinations. Up to the present time, inclusive of cases of which I have not kept records, I must have seen nearly 300 cases of this supposedly unusual malady.

It is not necessary for me to describe to you today the characteristics of the anhemolytic streptococcus found in the disease.

It has been given many names, none of which is apt. It is, therefore, best to call it *Streptococcus anhemolyticus* or, in English, anhemolytic streptococcus. The early names were *Streptococcus gracilis*, *Streptococcus viridans*, and *Streptococcus mitis*. When it was found that in a number of cases the non-hemolytic cocci cultured from the blood did not produce green color in the colonies, such organisms were called *Streptococcus albicans*. For a time I termed the organism *Streptococcus mitis*.

Anhemolytic streptococci are frequently found in tooth-sockets, roots of teeth, infected gums, in all parts of the throat, in diseased accessory sinuses, in uterine infections, in the normal intestinal tract, in infections of the bronchial tree, and in local infections in any part of the body, such infections being usually not of as severe a nature as those due to hemolytic streptococci. From all such places of origin the cardiac valves may be infected, but they are rarely affected unless previously diseased.

It is important for you to know that anhemolytic streptococci may be found in the blood in cases in which there is no evidence that the patient has developed a subacute streptococcus endocarditis. In a small number of cases of undoubted rheumatic fever anhemolytic streptococci have been found in the blood. At present it is believed that there is no proof that they are more than secondary invaders. Complement fixation tests proved negative in all such instances in which the test was tried. In subacute streptococcus endocarditis the complement-fixation test is practically always positive with the homologous organism. The cocci in the rheumatism cases, moreover, have certain peculiarities in a morphologic and biologic way.

Again, when a patient has a local infection due to non-hemolytic streptococci, bacteria may enter the blood-current and not infect the valve. Such observations have been made by Schottmueller, Rosenow, Schuerer, Thalmann, Libman and Aschner, and others. It must be evident to you that these facts are important from the standpoint of diagnosis and prognosis because they make us realize that the finding of an anhemolytic streptococcus in the blood does not of itself constitute a diagnosis of the dread disease which we are today dis-

cussing The clinical evidence must be carefully weighed If the organism is found over a prolonged period, and there is no active primary focus present, then one can usually be sure that one is dealing with a case of subacute streptococcus endocarditis, whether typical manifestations of the disease are present or not.

The disease occurs nearly always, as I have indicated, in people who have had a previous valvular defect In most of these patients there is a history of rheumatism, but the organism may attack a syphilitic or atherosclerotic valve Infection of the right side of the heart hardly ever occurs, and is then minimal I have seen several cases in which the previous defect was a congenital one, the lesion in all the cases that I can now recall being an open ductus arteriosus It is noteworthy that the infection occurs mostly in persons who did not know that they had a valve lesion, or knew it, but had no symptoms, or slight or moderate symptoms only It is unusual for a patient suffering from marked so-called decompensation to develop the disease Patients with organic tricuspid disease usually do not develop the disease The explanation is, I believe, that such patients are earlier decompensated I might say in passing that tricuspid disease is one of great interest, especially as regards prognosis, in cases of valvular disease, and that it needs much more study than has been devoted to it in the past

While the infections by the streptococci may arise from any of the foci I have mentioned above, and while such foci may represent not merely the presence of the cocci, but diseased processes due to them, the infections originating the disease are usually of a type that give no, or slight, local symptoms For that reason the onset of the disease is almost always insidious, and there is no definite history of a primary infection The earliest symptoms of the disease not infrequently resemble those supposed to be characteristic of influenza or an ordinary "cold," and therefore we are often told that the disease began with a "cold in the head" or an attack of influenza

The disease may occur at all ages, but is rare in childhood and in old age Of 150 cases of my own, tabulated by Dr Maurice Rashbaum, who has been of the greatest service in

collating the data, only 1 case occurred in a child under ten years of age, 4 between the ages of fifty and sixty, and 3 between the ages of sixty and seventy. Over one-half of all the cases occurred in patients in the second and third decades, and in these two periods the incidence was the same. The youngest case was eleven, the oldest sixty seven, years of age. Since Dr Rashbaum studied my cases for me I have seen a case in a child of five. Cautley describes a case in an infant. In a study of 180 cases we found 101 in males and 79 in females. Whether this predominance in males means anything or not I do not know.

### THE SYMPTOMS IN GENERAL

In discussing the symptoms of the disease you will note that, apart from those due to intercurrent conditions, they are produced in the following ways. We have first the symptoms due to the original valve defect, and of that disease as influenced by the fever of the disease, the anemia, the exhaustion, and the complications. These I call cardiac or, better, myocardial symptoms. Then there are the symptoms due to the infection. These are of two kinds: first, those due to the toxemia, and, second, those due to the vegetations in the valve. Due to the toxemia we have the fever with all its manifestations, including usually a marked anemia. Due to the change in the valves we have what I have termed the endocarditic symptoms. These include all manifestations due to breaking off of larger or smaller vegetations on the valves. Such symptoms are petechiæ, tender cutaneous nodules, embolisms, embolic aneurysms, and purpura. Purpura may, however, also be produced, I believe, by the toxemia and anemia. The subject of purpura in cardiac disease of all kinds needs elucidation.

The onset of the disease, as I have said before, is usually insidious. The patient may be up and around for a long time. We usually reckon the disease as lasting from four to eighteen months, but longer and much shorter cases have been observed by other authors and by myself. The earliest symptoms are of the greatest variety. In fact, we could spend all the time



at our disposal today in going over the many modes of onset of the clinical picture. I may later do this in a brief fashion. The most common symptoms at the onset are lassitude, vague pains, loss of appetite, feverishness, chills or chilliness, vertigo, headache, cough, and, less often, cardiac symptoms. The constant symptom in all the cases is fever. Occasionally the disease is acute in onset, the first symptoms being a high temperature, accompanied or not by a chill, or an embolism of one of the organs or of one of the peripheral vessels. It is very probable that in all such cases there has been a fairly long preceding period during which the patient was suffering from the infection, and either did not feel ill or did not feel ill enough to consult a physician. I remember seeing a woman who, ten days before being seen by me, walked almost ten miles in the Catskill Mountains in company with her physician. She took sick with vague abdominal symptoms, diarrhea, and fever, one or two days later, and was brought to New York on the day before that on which I saw her. She was suspected of having an atypical typhoid infection. Because of the presence of an exquisitely tender sternum without evident cause I examined her heart with great care, and finally satisfied myself that the mitral orifice was stenosed. After a prolonged search I found one petechia. A blood-culture was ordered, and the next day an anhemolytic streptococcus was found. On the same day the patient died with symptoms of pulmonary infarction.

The possibility of patients going around for a long time and attending to their duties and not realizing that they are sick is a very important one in connection with a part of this subject that will occupy us much in future conferences—namely, the bacteria-free stage of the disease. It explains how it is possible for us to encounter patients who have become spontaneously free of the infection and come to us only later with the after results of the infection.

The most frequent symptoms of the disease are the following: Chills, fever, sweating, anemia, emaciation, petechiæ, purpura, cardiac symptoms, renal phenomena, tender nodes, pulmonary symptoms, tender sternum, changes in the color of the face,

splenic enlargement, gastro-intestinal symptoms, cerebral disturbances, joint pains and joint swellings, and peculiar pains in various parts of the body. Changes are found in the background of the eye in some of the cases, and these I shall briefly describe.

#### FEVER, CHILLS SWEATS

The course of the fever is very variable. It is usually low at first and higher later. If one has the opportunity of observing the cases for a long period, beginning early in the disease, one often finds that the fever will at first be moderately elevated for a period of, say, a week or two, then for a few days come to a slightly lower level, then rise to a higher level than at the beginning, and after several such waves the temperature will finally reach 103° or 104° F, and have a tendency, at its highest, to remain near that level most of the time for a number of weeks. The fever is usually irregularly remittent, but at times intermittent. It is not uncommon to find little or no fever for a period of a few days or longer. Toward the end of the disease the fever is sometimes absent for two or three weeks. I have found this to have a greater tendency to occur in patients who have developed clinical evidences of renal insufficiency to such a marked extent that the diagnosis can be made from smelling the breath. Complications influence the temperature very considerably, embolisms in particular having a tendency to cause sharp rises.

An occasional chill may occur in the course of any case. A chill will often mark the occurrence of an embolism or the onset of an intercurrent disease. There are many cases in which no chills are observed at any time. On the other hand, there are cases characterized throughout by the occurrence of severe chills, sometimes two or more a day. I have been struck by the fact that cases which are characterized by the occurrence of frequent chills are often those in which the first evident symptoms of the disease are due to splenic infarction. In some cases the sudden rises and falls of temperature, with attendant chills, may be due to sharp bactericidal action of the blood-serum. Blood-culture studies should be made frequently in such cases,

before and after chills, to determine the validity of such an opinion

As in other diseases, chills occur very often after the use of any method of intravenous therapy, salt-water infusion, or any form of transfusion. If a chill has followed any method of intravenous treatment the temperature may fall to normal for from one to several days. It is interesting in this connection to draw attention to the observation of Kinsella and Swift, that the blood often becomes bacteria free for from one to several days after such a reaction has occurred.

The chills are usually followed by profuse sweating, but sweating constitutes in itself a very common and often an early symptom. This has frequently led to an erroneous diagnosis of tuberculosis being made.

### CARDIAC SYMPTOMS

Earlier I explained to you the difference between myocardial and endocarditic symptoms in cardiac disease. This differentiation, as I shall explain to you more fully in connection with cases in the bacteria-free stage, is of fundamental importance. In the bacteria-free stage one finds, on the whole, less endocarditic symptoms and more myocardial symptoms, that is, symptoms due to myocardial strain. The endocarditic symptoms I have named. The myocardial symptoms may occur in any case of disease of the heart, whether it be valvular, myocardial, or vascular in origin, in other words, whenever the heart muscle is strained. The myocardial symptoms are apt to be more marked in the bacteria-free stage than in the bacterial stage, and more marked late in the bacterial stage than early.

Dr. David MacDonald, in a splendid contribution on the etiology and the causes of cardiac insufficiency in cases of valvular disease, has listed so well the symptoms that we are wont to find when the heart muscle is weakened that I can do no better than copy his data. The myocardial symptoms are: Breathlessness (on exertion, or dyspnea, or orthopnea), edema (feet and ankles, feet and face, feet and abdomen, feet, face and abdomen, general anasarca), palpitation, bronchitis, cough with-

out expectoration, thoracic pain (precordial, right-sided, sense of constriction, angina like), general weakness, hemoptysis, anorexia, vomiting, epigastric pain, flatulence, nausea, gastric discomfort, headache, insomnia, giddiness, fainting attacks, cold extremities, feeling of impending dissolution, throbbing under right costal margins, epistaxis, noises in the head, and failing eyesight. This list of MacDonald's lacks certain symptoms. I shall not go into a discussion of all of them now, but wish to add the following Cyanosis, clubbing of the fingers, arrhythmia, feeling of pressure and pain in the region of the liver, tenderness of the liver, evidences of insufficiency of the functions of the liver, jaundice, and pulmonary edema. The tendency toward the development of venous thromboses, especially in cases of valvular disease, has been well brought out by Dr Welch in his learned contribution to the *Jacobi Festschrift*.

Any or many of these myocardial symptoms may be observed in patients suffering from subacute streptococcus endocarditis. The evidences of hepatic insufficiency are not usually present in the bacterial stage of the endocarditis cases, because, as stated above, the disease occurs less in decompensated individuals and infrequently where there is tricuspid disease present. The greatest tendency toward the development of hepatic symptoms is present when there is tricuspid disease present. The symptoms of less marked cardiac insufficiency are present in a number of cases early in the disease. But it is a remarkable fact that in many cases there are no evidences of cardiac insufficiency until late in the disease, and that they are due as much or more to the exhausted condition of the patient and to the anemia than to the changes in the heart as such. The endocarditic symptoms we will take up separately.

It is unusual for any new murmurs to develop in the course of the disease. If you look at specimens of hearts obtained from patients dying from this disease you will see why this is so. When the mitral valve is involved there is little or no tendency to ulceration, and the vegetations extend up on the wall of the auricle and involve the chordæ tendinæ. There is usually no tendency toward a blocking of the mitral orifice. When there

is aortic involvement ulceration may occur, but it is unusual. Ulceration occurs only when the vegetative process is extensive, and then any insufficiency caused by the ulceration is compensated for by the masses of vegetations. A mass of vegetations on an aortic flap may cause an increase in the loudness or roughness of a previously existing systolic murmur. At the mitral orifice previously existing systolic murmurs may increase in loudness or in area of distribution when the heart muscle becomes weakened. A systolic murmur in the pulmonary area may develop as in other cases of anemia or long-standing enfeebling disease. At postmortem examination the chordæ tendineæ are often found torn. Such torn chordæ tendineæ do not cause the auscultatory phenomena that have been ascribed to this lesion. The rapidity of the pulse depends much on the grade of severity of the fever and toxemia, and on the various complications. It may remain but little elevated for a long time. Arrhythmia is remarkably infrequent.

It is very unusual to find evidences of pericarditis in cases of subacute streptococcus endocarditis. When pericarditis occurs and there is present no extensive infarction of the heart muscle, to which the pericarditis is reactive, and there is no pneumonic lesion found, and the pericarditis is not the terminal pericarditis of a chronic nephritis, one must be suspicious of a mixed infection with the virus of rheumatism.

The heart muscle, as you know, contains lesions which are called Bracht-Wachter lesions, and which are located in the muscle-fibers themselves. Up to the present time there are no reports of changes that may be found by electrocardiographic studies. That the cardiac insufficiency may be due mainly to anemia is proved by the fact that transfusion may cause a remarkable increase in cardiac power, just as transfusion does in many cases of pernicious anemia.

### PULMONARY FEATURES

Cough is a very frequent symptom, even early in the disease. In some cases the patient has a severe spasmodic cough, although no gross changes may be found in the lungs. Such a cough may

be due to pulmonary congestion, for we encounter a similar cough in certain cases of mitral stenosis. I have thought that the violent cough might at times be due to irritation of the trachea at its bifurcation by the presence of enlarged tracheobronchial lymph nodes. It is quite the rule to find these nodes (inferior intertracheobronchial group of Poirier) enlarged in cases of infection of the valves of the heart, these being the nodes to which is brought the lymph return from the heart. You would be surprised at the autopsy table to see how large these nodes *may become*.

There is a tendency in the disease toward the development of bronchitis, and the sputum is apt to become hemorrhagic. Other conditions that are observed are bronchopneumonia, lobular pneumonia, lobar pneumonia,

ductus arteriosus was patent, and there were extensive vegetations on the wall of the pulmonary artery which was the seat of an aneurysm

Pleural effusions may occur secondarily to a pneumonia or an infarction, or may occur in the absence of a definite pulmonary focus. The fluid is clear, sometimes hemorrhagic. Pleurisy or pleural effusion may be caused by splenic infarction. Toward the end of the disease hydrothorax is apt to be present. This is more likely to occur if the anemia be profound. Pulmonary edema may occur in the course of the disease, but more often near the time of death.

### RENAL AND VESICAL SYMPTOMS

The clinical picture presented by the kidneys in cases of subacute streptococcus endocarditis has many points of interest. Embolism of the organ, as you know, is very common in this disease. We distinguish two forms of embolism, but they frequently occur together. The first type consists of embolism of larger vessels (macroscopic embolism), and the second, of vessels in the glomeruli (microscopic embolism), the latter constituting the remarkable characteristic lesion described by Loehlein, and then studied with great care, particularly in the bacteria-free cases, by Dr. Baehr.

The symptoms of the grosser infarctions may vary in severity from a very mild pain to violent spasms of pain, usually accompanied by hematuria. The kidney or kidneys may be found enlarged. Often there is marked tenderness present. The situation of the pain is usually the lumbar region, sometimes radiating down to the external genitalia. At times the pain is felt most in the flank or in the front of the abdomen. Bladder symptoms are frequent, consisting mainly of frequency of urination, usually accompanied by pain, tenesmus, pain in the hypogastrium, and sometimes retention of urine. When the pain is severe and accompanied by rigidity in the lumbar region an incorrect diagnosis of perinephritic abscess may be made. Sometimes the pain is felt mostly just above the crest of the ilium. When the pain occurs in this position it probably means, as

Curschmann has explained in another connection, that the lumbar nerves, especially the iliohypogastric nerve, are affected by lesions involving the posterior part of the capsule of the kidney

Vomiting is very common with renal infarctions. There are other varieties of the radiation of the pain and other accompanying symptoms that I will not now discuss. When the diagnosis is in doubt one can often make good use of the presence of Head's zones. The value for diagnosis of hyperalgesic areas in the skin was at first overestimated and is now underestimated. The method can often be used to the greatest advantage of the patient. The sensitive skin areas are particularly valuable if they occur in a patient not very sensitive to pain.

The presence of vesical symptoms has led to frequent errors in diagnosis. Cases of subacute streptococcus endocarditis have been mistaken for tuberculosis of the kidney and bladder, pyelonephritis, calculous kidney, and perinephritic abscess. In a number of instances operative procedures have been carried out, and I know of at least two cases in which a kidney was removed. If a mistaken diagnosis has been made before an operation, in such a case the surgeon, if he knows any pathology, will not remove such a kidney after exposing it, because the appearance is very characteristic. There are usually infarctions present of an ochre-yellow color, and the surface of the organ shows numerous fine hemorrhages, giving the appearance of the so-called flea bite kidney. This name, as far as I know, was first applied at Guy's Hospital.

I am reminded in this connection of a case in which the blood-cultures helped us in making positive a diagnosis of a streptococcus endocarditis, and in which later very severe renal symptoms developed and there was complete suppression of urine. A Ray examination was made, and there was found an irregular very dark shadow filling out the pelvis of the kidney on the left side. We were not quite convinced that the shadow represented a calculus and did not advise operation, which was also not to be thought of because of the severity of the patient's condition. At the autopsy there were found a general milary



tuberculosis, subacute streptococcus endocarditis, and no calculus. The shadow was due solely to the presence of blood. There was a small amount of fluid blood in the bladder.

The lesions in the glomeruli are very apt to be accompanied by the presence of erythrocytes in the urine. This finding is of some value for diagnosis. One must be careful, however, not to lay too much stress on this symptom, because, apart from other causes, it may be found in severe cases of rheumatic endocarditis. In searching for microscopic hematuria the middle part of a specimen is the most important. It is probable that gross hematuria may be produced by the glomerular infarctions as well as by the gross embolisms.

It is very common, even early in the disease, to find albumin and various forms of casts in the urine. These symptoms are apt to be more marked when there are present extensive embolisms or a glomerulonephritis, or a combination of both. As a result of the embolisms or of the glomerulonephritis, or of both, interstitial changes may occur. A real glomerulonephritis is more apt to occur in the influenzal cases. Marked evidences of renal insufficiency, however, only occasionally occur, and then, as a rule, only shortly before the patient dies. Usually the patient succumbs before the renal condition is sufficiently advanced to cause renal inadequacy. When such a condition does supervene the symptoms are the usual ones, and there is a marked reduction in or absence of phthalein excretion, and changes in the blood chemistry. In women the menses are apt to be lost in the course of the disease.

#### SYMPTOMS DUE TO SPLENIC CHANGES

The spleen is often enlarged and palpable and may be soft or hard. When it is very large mistakes in diagnosis are apt to be made, the patient being supposed to be suffering from splenic anemia, Banti's disease, pseudoleukemia, or some other form of splenic disease. Infarctions are very frequent, and on their supervention cause severe pain and vomiting. Such symptoms may usher in the disease. The pain at the onset of an infarction is due in part to stretching of the peritoneal covering of the viscus,

and later to perisplenitis, which may at times be detected by the presence of a friction rub that can be palpated or auscultated

While the pain is usually felt in the splenic area, and is then accompanied, as a rule, by marked local rigidity and tenderness, it may be felt also or only in the cardiac area, particularly in the lower part. At times there is severe pain somewhere in the region of the left shoulder. Whether there is pain in the shoulder region or not, the left trapezius muscle is usually tender if the infarction is at all severe. This symptom is brought out by squeezing the muscle, with various degrees of pressure, in the supraclavicular region

Infarctions may be very extensive and break down and even rupture. I have seen one case in which there was extensive infarction of the spleen and secondary thrombophlebitis of the splenic vein. Large softening infarcts may give rise to wide fluctuations in temperature at a time when the patient's temperature is running a rather mild course. Although polymorphonuclear leukocytes may be present in such softened lesions, they are not abundant and true suppuration does not occur. It is a feature of the disease, known for a long time, that pus formation does not occur in any of the lesions, this phenomenon, however, being very frequent in cases of bacterial endocarditis running an acute course—the so-called acute malignant endocarditis

Horder has given an interesting explanation of the fact that the spleen may not be felt in certain cases even when it is much enlarged. He believes that it may be due to the presence of a well-developed costosplenic ligament on which the organ rests

#### GASTRO-INTESTINAL SYMPTOMS THE LIVER, ABDOMINAL PAINS

The gastro-intestinal symptoms are conspicuous in some cases, especially in the early part of the history. There is often distress after eating, pressure in the epigastrium, lack of appetite, nausea and vomiting, or symptoms like those usually ascribed to hyperchlorhydria. These symptoms may sometimes be so pronounced that the patient is suspected of suffering from malignant disease of the stomach or a serious disease of the

intra-abdominal lymph-nodes Whether achylia occurs I do not know, but I have seen it at least twice in cases in the bacteria-free stage Gastro-intestinal symptoms may, of course, be produced reflexly from congestion of the liver or infarction of the spleen or kidney There are often inexplicable pains in the epigastrium, and these may occur in a severe form early in the disease Diarrhea is an unusual symptom

The liver is often enlarged, due to the changes incident to toxemia and to congestion If the enlargement is marked the organ may become tender Occasionally the tenderness is very marked, and there is also local or general abdominal rigidity and vomiting Under such conditions the right trapezius muscle may become tender Jaundice is a very unusual symptom, as are also the various symptoms that occur in hepatic insufficiency

Pains in various parts of the abdomen are quite frequent. I have already described to you some of them in discussing the symptoms produced by involvement of the larger abdominal organs Pains may also be produced by embolic aneurysms which occur as frequently in the mesenteric vessels as in any other arteries in the body, except perhaps those of the brain. Pains without assignable cause may occur in any part of the abdomen Horder believes that such pains may be due to small omental hemorrhages

### BLOOD CHANGES

Anemia is a very characteristic symptom of the disease It is of the type of a secondary anemia, and often becomes quite intense as the disease goes on I have not encountered blood findings like those seen in pernicious anemia The hemoglobin may sink below 20 per cent The leukocytes may be hardly increased in number or there may be a high count with a decided increase in polymorphonuclear cells The count may be normal or below normal, with an increase in the polymorphonuclear cells or in the lymphocytes One may find a leukocyte count of 5000 with 40 per cent polymorphonuclears, or 3300 with 52 per cent lymphocytes, or 9400 with 80 per cent.

polymorphonuclears I have seen counts as high as 26,500 with 86 per cent. polymorphonuclear leukocytes, but the highest count was 48,000 with 67 per cent. This last case was the one of splenic infarction and thrombophlebitis of the splenic vein to which I have already referred

The anemia of the disease is, I believe, due to destruction of erythrocytes by the cocci, even though they are called an-hemolytic, and to changes in the bone marrow or in its functional capacity. The cocci of the disease are called anhemolytic because, in blood-plates, there is no area of clearing about them. This, however, is not a real proof of inability to cause hemolysis. The proof of this I shall give you on another occasion.

#### CUTANEOUS SYMPTOMS COLOR, PURPURA, ERYTHEMATOUS ERUPTIONS, PETECHIÆ, TENDER EMBOLIC LESIONS

The cutaneous phenomena of the disease are of great interest, and give us some of the most valuable information for the purpose of diagnosis. The color of the face often becomes pallid in the course of the disease and has a tendency to have a dirty whitish color or, more commonly, a *café au lait* color. The patient often has a tired look. In cases in the bacteria free stage the patient may develop an intense brown pigmentation of the face which is quite characteristic. In one patient in whom we found streptococci in the blood, and thereby knew we were dealing with a case in the active stage of the disease, it was noted that the face was of the deep brown color found only in the bacteria free stage. I was suspicious that the case might be one of recurrent infection in a bacteria free stage, and this diagnosis was confirmed at autopsy. When at a later time we go further into the question of pigmentation of the face in cases in the bacteria free stage I shall draw attention to the difficulties that arise because of the peculiar pigmentation of the face found in patients with tricuspid disease.

There appears rarely a curious papulo-erythematous, rather dark red eruption on the bridge of the nose and extending over both sides of the face in butterfly fashion. Patients who are treated in the cold open air are more apt to present this symp-

tom, or to present it in a marked form. The eruption is also then apt to have a tinge quite bluish in color.

Purpura is a rather infrequent symptom in the bacterial stage. Through the kindness of Dr. Fordyce I can show you today a photograph of a case with the most extensive purpura that I have ever seen in this disease. It is interesting to note that the lesions on the face are distributed very much as the papulo-erythematous eruption that I have just mentioned.

A peculiar form of lymphangitis, the so-called rheumatic lymphangitis of Wilms, has been described in one case by Steinert. I have not encountered this lesion. Erythematous rashes in the group of erythema multiforme may occasionally be seen, but I cannot recall any case with a definite erythema nodosum of the classic type.

Recently, through the kindness of Dr. Lawrason Brown, I saw a case with a mild form of the papulo-erythematous facial eruption, and lesions on the forearms resembling erythema nodosum. The lesions, however, were very small. They were not tender. Scattered over the body, especially on the abdomen, were small lesions, some almost as small as roseolæ.

One of the most interesting and important symptoms of subacute streptococcus endocarditis is the petechial eruption. I have found petechiæ present in over 80 per cent. of the cases. They may be entirely absent or few in number, or so abundant that they are found over the entire body. They are apt to come out in crops, each crop lasting several days. When they fade out they may leave a yellowish-brown stain for several days.

It is important when looking for petechiæ to examine particularly the conjunctival mucous membrane of the upper and lower lids, the supraclavicular and lateral cervical regions, the buccal mucous membrane, and the fundus of the eye. When the lesions are found in the conjunctiva, concerning the petechial nature of which one is in doubt, it is a good plan to squeeze the lid at its margins, just as one presses on the skin to determine whether a lesion is petechial or not. If the particular conjunctival lesion is a petechia, it will stand out sharply against the anemic conjunctival mucosa. In looking for petechiæ on

the buccal mucous membrane one must be careful not to mistake traumatic lesions for embolic petechiæ. One must be particularly cautious in deciding about lesions of the buccal mucosa near the labial commissures, because many people have a tendency to bite the mucous membrane there and produce small hemorrhages.

The petechiæ found in the bacterial stage are apt to be a bit lighter than those found in the bacteria free stage. It is of great value to note the color of the petechiæ very closely because petechiæ resembling those found in this disease may be found in cases of cerebrospinal meningitis, but they are apt to have a somewhat bluish tinge. Splashes of hemorrhage in the conjunctival mucous membrane unaccompanied by general purpura are not usually found in the endocarditic cases, but are often found in epidemic cerebrospinal meningitis. Petechiæ with white centers are the most vital for diagnosis, because then one can have no doubt that the lesion is an embolic one, and not a symptom of a purpuric nature. It is especially important (and this holds especially true for conjunctival lesions) to note whether the central white part is elevated or not, because such elevation does not occur in subacute streptococcus endocarditis. Petechiæ with elevated white centers are pathognomonic of infection by staphylococci and usually by the *Staphylococcus aureus*. They are really miliary abscesses surrounded by a zone of hemorrhage.

Of the greatest importance are the painful or tender nodes to which particular attention has been drawn by Sir William Osler. It appears that these nodes were observed by Rapin in 1870, 1875, 1891, and 1901. Rapin states that Senhouse Kirkes, working under Virchow, in 1852-53 also called attention to these nodes. Heubner is supposed to have noted them in 1879. Little attention, however, was paid to these nodes until Sir William Osler emphasized their importance, and Parkes Weber has suggested that they be called "Osler's sign." In France this lesion is called *nodosités cutanées éphémères*. My attention was first called to these nodes as being of probable importance in this disease by Dr. Manges several years before the paper by Osler.

appeared The nodes occurred in 7 of the 10 cases reported by Osler, and in at least 50 per cent of the cases that I have observed The description given by Osler is as follows

"The nodes appear at intervals as small swollen areas, some the size of a petechia and others as large as  $1\frac{1}{2}$  cm in diameter They are raised, red, with a whitish spot in the center They may pass away in a few hours, but usually last one day or longer The most common site is upon the tip of the finger, which may be slightly swollen They also occur in the pads of the fingers and toes, thenar and hypothenar eminences, sides of the fingers, and the skin of the lower part of the arm In one case they occurred in the skin of the flank They are never hemorrhagic. Sometimes they are of a vivid pink hue with a slightly opaque center "

In my experience certain other forms of these lesions are to be seen For instance, there may be erythematous areas without the formation of the nodule Such an area may cover the whole pad of a toe or be pin-point in size Some of the large areas are of a paler color, and in them can be seen darker erythematous lesions of the size of a pin-point No matter how small the lesion is, it is always tender when recent This usually holds true even if the patient is not sensitive to pain Sometimes the lesions are quite bluish or purplish in color One also encounters anemic areas in the skin, these are usually accompanied by nodule formation Such lesions are also always tender A whole terminal phalanx of a hand or foot may be anemic, swollen and tender, or dusky red or purplish and swollen and tender Sometimes one sees an anemic nodule surrounded by a delicate areola of hyperemia A week may elapse before all the tenderness has disappeared from such a lesion Most of the lesions disappear within three or four days

All these forms of lesions are of great diagnostic import, for, according to my experience, one finds them occurring only in the disease in question In cases of acute bacterial endocarditis lesions may be found in the palms and soles that may be mistaken by inexperienced observers for the cutaneous phenomena of subacute endocarditis These were described in

particular by Dr Edward G Janeway as "small hemorrhages in the palms and soles with slightly nodular character" The latter lesions are not tender

#### VASCULAR FEATURES EMBOLISMS, EMBOLIC ANEURYSMS, PHLEBITIS

The main clinical features, as regards the vascular system, are the embolisms and embolic aneurysms The petechiæ, the tender cutaneous nodules, and the erythema, theoretically, should be included in a discussion of the vascular phenomena, as they are due to embolisms of capillaries and arterioles These lesions, however, are of more interest clinically as cutaneous symptoms, and I have, therefore, grouped them under that category

The most common location of the embolisms is in the brain Of 50 instances of embolism tabulated by Dr Rashbaum and myself, 27 were intracerebral The next most common seat was the popliteal artery (10 cases), and the next the brachial artery (3 cases) Any artery in the body may be involved I have observed embolism of the following arteries femoral, mesenteric, temporal, hepatic, radial, ulnar, uterine, coronary, and the central artery of the retina Embolism of the last named artery is rare, but it may mark the clinical onset of the disease. Horder describes gastric embolisms, but I have not seen them. It would take us too far afield to review the clinical pictures produced by the embolisms in various parts of the body You will find an exhaustive account of them in the remarkable monograph on "Embolism and Thrombosis," in the Allbutt-Rolleston System of Medicine, by Dr Welch.

Embolic aneurysm seems to be more frequent in subacute streptococcus endocarditis than in other forms of infection. I am sorry I cannot discuss these aneurysms in detail today The first embolic aneurysms that were described in the literature were supposed to be produced by impaction on the wall of a blood vessel by firm calcareous material thrown off from one of the valves of the heart. Osler in 1885 described a remarkable case of infective aneurysm of the walls of the aorta which he



believed to be bacterial in origin. A few years after the paper by Osler, in 1888, Eppinger described a series of cases of embolic aneurysms which were all of bacterial origin. It was then believed that all embolic aneurysms were mycotic in nature.

In 1905 I presented evidence that makes it definite that two types of aneurysm may occur, one due to impact on the wall of a vessel by non-infective material and the other due to infection of the vessel by material containing bacteria. It has generally been considered that infection of the wall of the vessel occurred due to embolism in its lumen, but I believe the embolism occurs more often by the way of the vasa vasorum than is usually believed. While the embolism usually consists of bits or pieces of the vegetations in the valves, smaller lesions may conceivably be produced by clumps of cocci. Occasionally we can feel small nodular thickenings along a peripheral vessel. These probably represent inflammatory areas or minute embolic aneurysms. I have had no opportunity of studying these under the microscope. In the cases of endocarditis in the bacterial stage the aneurysms that occur are naturally always due to infective material. It is only in the cases in the bacteria free stage that one encounters the non-infective embolic types of aneurysm, and this is the only condition in which it is ever found as far as I know.

The mycotic aneurysms occur particularly at the bifurcation of vessels that lie in soft tissue. The valves of the heart especially the mitral valves and the sinuses of Valves, may be the site of such aneurysms. They produce symptoms by pressure on surrounding parts or by rupture with resulting hemorrhage. When this rupture occurs into the tissue of one of the limbs a false aneurysm is produced. Perforation may occur into a vein, with the production of an arteriovenous aneurysm. In the abdominal cavity they produce pain and possibly intraperitoneal hemorrhage. The symptoms produced by rupture of embolic cerebral aneurysms I shall briefly describe later.

The phenomena produced by these aneurysms may sometimes be quite extraordinary. In one case described by Horder there

were two aneurysms of the superior mesenteric artery which were so large that they could be felt as hard nodules by rectal palpation. In another case described by Hegler there was an aneurysm of one of the intrahepatic branches of the hepatic artery. This had ruptured into the liver substance and there then followed a rupture through the peritoneal coat of the liver into the peritoneal cavity. Among other examples of embolic aneurysms that I have encountered in cases of subacute streptococcus endocarditis there was a remarkable one in the femoral artery in a boy about sixteen years of age. He was admitted to the hospital with a diagnosis of osteomyelitis because of swelling in the thigh, fever, tenderness, and leukocytosis. The first impression I had of the case was that it might be a neoplasm of the left kidney with metastasis in the femur, occurring in a boy with aortic insufficiency. But when I found that he had a large spleen and was very anemic I came to the conclusion that he was probably suffering from infection of the valves of the heart, and suggested that he might have an embolic aneurysm of the femoral artery with rupture into the soft parts. At autopsy we found extensive erosion of the femur, which explained the violent pain from which he had suffered. The blood-cultures during life had remained sterile. At the postmortem examination there were characteristic lesions of subacute streptococcus endocarditis present, most of which were organizing or were completely organized. In the more recent lesions there were found, on microscopic examination, streptococci which could not be cultured. You will find a case like this described in the Quarterly Journal of Medicine by one of our former interns. It is the same case as the one about which I have told you. The interpretation given by the writer is not correct. Had I known that the material was to be used, the case would have been correctly put on record.

As regards the veins, the only lesions of interest are phlebitis and arteriovenous aneurysm. Phlebitis is an uncommon symptom. It usually occurs late, but may be the first symptom. Whether, besides being due to the causes to which it is usually ascribed, it is ever caused by metastatic infection of the wall of

the vein by the cocci of the disease I do not know I can remember one case of arteriovenous aneurysm of the femoral artery produced in the manner just described to you

#### OSSEOUS SYMPTOMS THE TENDER STERNUM BONE PAINS

As regards symptoms in the osseous system, the most interesting phenomena are the tenderness of the lower sternum, to which I drew attention in 1910, and the bone pains The sternal tenderness does not occur in all cases, and is apt to be a late rather than an early symptom It may occur in the absence of any marked anemia In the bacteria-free stage it is a much more constant symptom It must be remembered that there exists a number of causes for tenderness of the sternum, and I do not wish to be understood as stating that a tender sternum means that you are dealing with a case of endocarditis But when you find it and do not readily find an explanation for it you must think of endocarditis as a possible cause Earlier this afternoon I sketched for you a case in which this symptom led to a correct diagnosis I might interpolate here a fact to which we will refer when discussing certain aspects of valvular disease, namely, that in tricuspid disease the sternum is often tender, and that in the presence of marked dyspnea the sternum is less apt to be sensitive

In testing for tenderness of the sternum it is best to tap the upper sternum and then the lower with the same force so as to get the comparison If the lower is not sensitive, one increases the force of the tapping of the upper and lower sternum Direct pressure against the sternum is not advisable because such pressure against any bone is apt to be painful This sternal tenderness is more significant if it occurs in a patient not very sensitive to pain It is a comparatively simple matter to tell if a patient is sensitive to pain or not In the majority of people pressure on the styloid process is rather painful In some, pressure on the styloid process is exquisitely painful, in others, only slightly so, and in some there is no pain at all It is in the latter class that the symptom of pain or tenderness is more valuable for diagnosis I shall discuss this matter more

fully on another occasion. I would, however, suggest now that if you wish to use this test you first always press on the mastoid process for a control observation, but you must press directly against the bone and not rub the skin over the bone, as that may give you deceptive tenderness. This test for sensitiveness of patients is simple, but of the greatest value in making diagnoses as well as determining how a patient will stand operations under local anesthesia.

The sternal tenderness is probably due to active regeneration in the bone-marrow. In several fatal cases in which we could obtain material from the marrow of the long bones we have found such regeneration. Its absence cannot always be explained. In some cases there is a lack of sensitiveness on the part of the patient, and in some the lower sternum is very narrow and quite thin, and, therefore, there can be but little medullary tissue present.

Severe pains may be located in any of the bones. Horder described a case in which the most prominent symptom was in the sacrum, and another with ischialgia. Some time ago I saw a case with Dr. Louna in which the blood-culture showed an anhemolytic streptococcus and in which we believed an endocarditis was present, but in which the pain in the upper end of the femur was so severe that we considered it justifiable to make an exploratory incision. The periosteum was found slightly loosened, but there was no lesion in the bone-marrow except for some hyperemia. Lenhartz was of the belief that many of the pains in the limbs felt in the course of cases of subacute streptococcus endocarditis were located in the periosteum of various bones. Recently I saw a child that was under the care of Dr. J. Mandelbaum and Dr. Otto Hensel, the case was believed by them to be one of subacute streptococcus endocarditis, and after repeated trials an anhemolytic streptococcus was found in the blood. The child developed two kyphoses. Such a lesion I had not seen before nor have I found it in the literature. Schoene speaks of "metastases in the spleen, joints, and vertebrae," but does not give any account of the symptomatology of such vertebral changes.

## CEREBRAL SYMPTOMS PAINS

Cerebral symptoms are quite common in the course of the disease. A curious early symptom is vertigo, which has been present in a few of my cases. Such vertigo may occur on arising in the morning or after exertion. In one patient, who had fever and attacks of vertigo every morning on arising, Dr Joseph Rosenthal of Brooklyn made the diagnosis by finding a small embolic tender nodule hidden in the web between the big toe and the second toe of the left foot. The blood-culture was then found positive on a number of occasions.

Very common symptoms are headache, irritability, and insomnia, it is not uncommon, especially toward the end of the disease, for the patient to develop delirium, stupor, or coma. There may be extensive hemorrhages into the brain or into the ventricle or the subarachnoid spaces, due mainly to the rupture of embolic aneurysms. Intraventricular and subarachnoid hemorrhages produce a symptom-complex resembling a meningitis. There is severe pain in the head, stupor, coma, or occasionally convulsions, rigidity of the neck, some hyperesthesia, and Kernig's sign. If the patient becomes unconscious and regains consciousness he is apt to be more or less delirious. There may be paralysis of the extrinsic or intrinsic eye muscles. The patient need not die because of such a hemorrhage. In fact, it can occur more than once in the same patient. In a bacteria-free case I saw the patient recover from a severe hemorrhage of this kind and live for over two years more, when he died of cerebral embolism.

Lumbar puncture in such cases reveals a bloody fluid. If you are in doubt as to whether such blood admixture in the fluid is due to traumatism from inserting the needle or was present in the fluid before the puncture was made it is quite simple to arrive at the truth. As a rule, such cases are not punctured until twelve to twenty-four hours have elapsed from the time of the onset of symptoms. By that time there is a lymphocytosis in the fluid. You ought then to make a differential blood count at the time you make your puncture, and if you find a higher lymphocyte count in the bloody fluid removed

from the spinal canal than in the circulating blood, you can be sure the blood was present before you made the puncture. There are other aids for this diagnosis, but the method I have given you usually suffices.

Cerebral embolism, as I have already told you, is of very frequent occurrence. These emboli give the usual symptoms, and the clinical picture will, of course, be dependent on the position of the embolus. In one case having marked cerebral symptoms Steinert found an aseptic polynuclear meningitis, for which no cause could be found at the postmortem examination which was performed six weeks after the meningeal symptoms had subsided. Various forms of paresis or paralysis have been described. Apart from ocular paralyzes there has been described facial paralysis, auditory paralysis (increasing deafness, Schottmüller), and hypoglossus involvement causing hemiparesis and atrophy of the tongue. I have not seen chorea in any case. Once I observed a very interesting case of rheumatic fever with chorea which was followed within a few weeks by a fatal attack of subacute streptococcus endocarditis lasting several months, during which period chorea was absent. This case shows, like many others, the differences in the clinical pictures of rheumatic and subacute streptococcus endocarditis.

Pains in various parts of the body, as you have already been able to judge for yourself, occur with the greatest frequency and are due to a variety of causes. They may be due to changes in joints, bones, periosteum or attachment of muscles to periosteum, to aneurysms, to embolic nodes, and to infarcts of the kidney or the spleen. The remarkable gastric and lower abdominal pains have already been discussed. Severe epigastric pains are not at all uncommon in cases of uncomplicated mitral stenosis in young people. Epigastric pains in endocarditis cases frequently occur when there is no mitral stenosis present.

Sometimes the pains seem to be neural in origin. I have seen at least one case in which the pain was dependent upon anemia. This occurred in a woman who had a fairly well marked form of the disease and who complained of a deep-seated pain in the right orbit. When her hemoglobin dropped as low as 39 per

cent it was decided to perform a transfusion. Within a few days the hemoglobin had risen to over 60 per cent and the pain in the orbit disappeared, to return several months later, when the hemoglobin again dropped to 41 per cent. This observation would lead us to believe that the old idea that there exists an anemic neuralgia is correct. Another pain that occurs in the disease and in cases that I have particularly noted, at the onset, is a severe pain in the small of the back. It is remarkable to think that a patient can be walking around with a disease that is nearly always fatal, and have no other symptom but this pain, usually mistaken for a lumbago.

There are other remarkable unexplained localizations of very severe pain. For example, in one case there was a violent tearing pain in the side of the face. In the case of a man that came from Rio de Janeiro, who was supposed to be suffering from some tropical disease, the only symptom besides fever was an excruciating pain just below Poupart's ligament on the right side. There were no objective findings. The patient presented evidence of a valvular defect and had some temperature, and as we have made it a rule to make a blood-culture in every case of valvular defect in which fever was present, and particularly if some severe pain was complained of in some part of the body, we followed the routine in this case, and streptococci were found in the blood. The patient later developed many typical symptoms of the disease and finally succumbed.

#### ARTHRITIC SYMPTOMS EDEMA, GANGRENE

Swelling of joints or peri-articular swellings are not infrequent, and the patients often complain of arthritic or peri-artritic pains. All these phenomena, however, are milder than in cases of rheumatic fever. Lenhartz has characterized many of these pains as being "more or less marked rheumatic pains located less in the joints and more in the muscular attachments nearby, or in the periosteum of the long bones." He states also that there are occasionally only very localized spots of pain that can be covered by the tips of a finger.

As a rule, the joint does not look as if it were the seat of an

active inflammation, redness over the joint is not usually found, and when it occurs it is important to ascertain if the patient is not suffering from a mixed infection with the virus of rheumatic fever. In one case in the literature the knee-joint was aspirated, and a pale cloudy fluid found, which was sterile and contained almost entirely lymphocytes.

Edema of the extremities may be slightly marked early in the disease, but is much more frequent later. It is usually due partly to cardiac weakness and partly to anemia, and is usually a soft edema. If venous thromboses are also present the edema is apt to be firmer. General edema may occur. This is more commonly due to the anemia than to nephritis. In the influenzal cases we are much more likely to have a general edema of nephritic origin. Gangrene of the extremities, rarely of other parts, may occur, due to embolism of peripheral vessels.

#### OCULAR CHANGES

The ocular phenomena are of considerable interest and should always be looked for when making the diagnosis. The most common finding is petechiæ in the fundus, or occasionally small hemorrhages. On one occasion, while the fundus of a case of streptococcus endocarditis was being examined by Dr Percy Fridenberg, we had the unusual opportunity of seeing a hemorrhage occurring in the fundus of the eye. I have never seen iritis or iridocyclitis develop—a sharp contrast to the experience in cases of rheumatic and acuto bacterial endocarditis.

The white or yellowish white spots first described by von Roth, and generally known as Roth's spots, and which are not infrequent in cases of severe general infection by the ordinary pyogenic organisms, and which, therefore, are not infrequently found in the fundus in cases of acute bacterial endocarditis, are very unusual in the disease we are discussing today. Amblyopia or central scotoma may occur, due to embolism. Strabismus naturally will be found if the eye muscles are involved. Steinert described one case of irregular diffuse edema of the fundus. A very important symptom is optic neuritis. Falconer in the course of three years studied 15 cases, and found optic neuritis



in 5 In 4 of these 5 cases there were also recurrent retinal hemorrhages The neuritis was bilateral in all the cases but one, in this case, however, there was an opacity in the other eye In none of these cases was there visual disturbance The condition was looked for to help establish a diagnosis of subacute streptococcus endocarditis, and in 2 cases the diagnosis was based on this finding Falconer believes that the neuritis is toxic in origin

### MODE OF ONSET

Now that you have heard most of the symptoms of the disease described, it will probably interest you if I indicate briefly the great variety in the modes of onset in the disease You will then appreciate how carefully you must be on the lookout for the disease, especially in every case of valvular defect in which fever is present, and in which you have no proof that the cause of the fever is elsewhere than in the cardiac valves

- 1 Fever, with chilliness and sweats, and headache and drowsiness, like the onset of typhoid fever

- 2 Intermittent fever and chill, resembling malaria

- 3 Like influenza, with headache, general pains, malaise, weakness, and nasal symptoms

- 4 Fever alone

- 5 Resembling tuberculosis of the lungs, with fever, cough, loss of flesh, sweats, pain in the chest, weakness, and perhaps hemoptysis

- 6 Like tonsillitis, with pain in the neck and swelling of the tonsils

- 7 Simulating rheumatic fever, the joint pains constituting the most marked symptom

- 8 A tender cutaneous node may be the first symptom of the disease Occasionally such a node is incised under the mistaken diagnosis of paronychia

- 9 There may be general weakness, loss of weight, pain in the limbs and abdomen, depression, irritability, and insomnia, and a diagnosis of neurasthenia may be made until the presence of fever is detected

- 10 Severe pain localized somewhere in the body, for in-

stance, in the back or thighs, or inguinal region, or limbs, or abdomen, or extending from the side of the abdomen down the side of the thigh, or a tearing pain in the scalp and face, or a severe pain located at the site of the sacrosciatic notch.

11 There is a renovesical type of onset, with pain in back or hematuria and bladder symptoms

12 Evidences of myocardial insufficiency may be the early symptoms—dyspnea, palpitation, and perhaps edema of the legs

13 An aneurysm may be the first manifestation—I have described to you such a case

14 Embolism in a limb, a cerebral embolism, or a closure of the central artery of the retina

15 Occasionally a case has as its first marked symptom pain in the right hypochondrium, and local rigidity and tenderness, and the case is suspected of being one of abscess of the liver, or subphrenic abscess

16 In one instance a phlebitis of the lower limb was the first symptom of which the patient complained

17 Gastro-intestinal symptoms, such as vomiting, distress after eating, loss of appetite, or complaint of hyperacidity, may make the patient feel that he is not well.

18 Abdominal pains may be very marked at the onset and the clinical picture may resemble that of appendicitis I have seen 4 patients in whom the appendix was removed because of an error in diagnosis

19 Infarction of the spleen may cause a stormy beginning of a case

20 Basal hemorrhage may occur early in the clinical picture and the case be mistaken for a meningitis

21 Vertigo, either on ascending stairs or on awakening in the morning, is rarely the first complaint

22 Occasionally the disease begins in the postpartum period The patient is then suspected of suffering from an ordinary postpartum infection, when, in reality, she is suffering from subacute streptococcus endocarditis, and the disease was latent until the postpartum period In this connection I must remind

you of the statement I made when we first met today, that to find an anhemolytic streptococcus in the blood-current does not make it sure that the patient has an infection of a valve. As far as the literature is concerned a not uncommon origin of such a general infection is the uterus. It is, therefore, exceedingly important in cases in which the uterus is apparently the cause of an infection to determine whether there is a general infection from the uterus without infection of the valve, or whether the patient is suffering from a previously undiscovered subacute streptococcus endocarditis of which the origin is not in the uterus. Help could be obtained by a careful scrutiny of the history, by the examination of the uterine secretions, and by a search for the symptoms that are rather characteristic of infection of the valves by anhemolytic streptococci (especially tender nodes).

#### MANNER OF TERMINATION OF THE DISEASE

Subacute streptococcus endocarditis is a disease that is almost uniformly fatal. In the last few years I have seen four recoveries in definite cases, all with positive blood-cultures. Several times I have seen the blood-cultures become negative, but these patients all died of the results of the infection. Death may be caused in a variety of ways. A frequent cause of the fatal outcome is cardiac insufficiency from exhaustion, generally with pulmonary edema. Cerebral symptoms due to embolism or cerebral hemorrhage are quite often the final manifestations. Other causes of death are embolisms, pulmonary infarction, uremia, progressive anemia, and renal insufficiency. In a certain number of cases an intercurrent lobar pneumonia cuts short a case which looked as if it would last for some time still. Occasionally a miliary tuberculosis of the lung or a general miliary tuberculosis cuts the disease short. Horder believes that the fatal termination may be due to rupture of an aneurysm of a valve, or perforation of the ventricular or auricular septum. I have never seen perforations of these septa in subacute cases, nor are there any records of such a lesion in the literature. As regards aneurysms of valves, I have never seen death due to a

rupture of them Aneurysms of the sinuses of Valsalva might cause death by rupture, particularly into the pericardium

#### ASSOCIATION WITH OTHER DISEASES SURGICAL RELATIONSHIPS. THE DIAGNOSTIC SYMPTOMS

As you will have noted, the disease is not infrequently associated with other diseases, and there are aspects of the disease that have an important surgical relationship The diseases with which we have found the condition associated are mainly tuberculosis and lobar pneumonia The former association is much the more infrequent. That the disease has important relationship to rheumatic fever is evident from the fact that while valvular defects due to lues or to atherosclerosis may become infected, it is particularly the valvular defect due to the rheumatic virus that is the main seat of predilection The frequency of luetic compared to that of rheumatic valvular disease is much greater than the relative frequency of subacute streptococcus endocarditis in the two types of valvular defect Apart from this consideration, mixed infections may occur, that is, the virus of rheumatism or the syphilitic virus may be active at a time when the valvular defect due to an old obsolescent infection is infected by the streptococci How often such active infections coexist I do not know In one case at post-mortem examination we found the characteristic lesions of a recent rheumatic endocarditis on the mitral valve and in the heart muscle, and the evidences of subacute streptococcus endocarditis on the aortic valve In cases of streptococcus endocarditis occurring in luetic valves I have thus far only found symptoms of the lues (apart from those due to the aortitis or aortic insufficiency) in 2 cases In one, cerebrospinal lues was manifest, in the other, paresis

The surgical relationships of the disease have been briefly indicated to you I shall not discuss them any further, but shall mention the main conditions that may be thought to be present and be in need of surgical relief These are abscess of the spleen, subphrenic abscess, liver abscess, appendicitis, pyelonephritis, renal calculus, tuberculosis of the bladder perineph-

ritic abscess, and osteomyelitis. That the gangrene due to an embolism in the course of the disease or that an aneurysm may need the advice and help of a surgeon is self-evident.

A few years ago I had the opportunity of seeing a patient who was supposed to be suffering from anemia due to bleeding from fibromyomata of the uterus, and a systolic murmur found at the apex was supposed to be anemic in origin. As the patient had not bled for several months before the time that I saw her, and was complaining of pain in the small of the back, it was suspected the fibromyoma might have undergone malignant change, and I was asked to give an opinion on this point. On examining the heart I could not be sure whether the murmur which I heard indicated an organic insufficiency or not, but I rather felt that there was an organic mitral insufficiency present. I examined the patient very carefully, and near the tip of one finger I found a small red tender lesion that I considered to belong in the group of cutaneous lesions characteristic of the endocarditic cases. The patient insisted that the lesion was produced by the prick of a sewing needle. A blood-culture made on the following day revealed an anhemolytic streptococcus, and a few days later the patient's body was almost covered by petechiæ.

We will not have time today to go further into this subject or to take up the extensive question of differential diagnosis. I should like to have taken up with you the differentiation from rheumatic endocarditis as far as our present knowledge allows. The diagnosis as between the bacterial and bacteria-free stages may need careful study in those cases in the active stage which are not very marked and in which blood-cultures remain negative for a time or permanently, although bacteria are plentiful in the valve—in other words, in cases in which we fail to cultivate organisms that are present in the blood. It will be unwise, however, to take up this question until you have had demonstrated to you cases in the bacteria-free stage.

You may have gained the impression from the clinical picture as I have unfolded it to you that every case has a great variety of symptoms and of what I might call clinical upsets.

Many cases have the general toxemic phenomena alone for quite long periods along with lesser marked endocarditic or myocardial symptoms. But in any case, marked endocarditic symptoms may complicate the clinical picture at any time. Before closing I should like to again mention the symptoms that are the most important from a diagnostic standpoint. These are fever, petechiæ, tender cutaneous erythema or nodes, anemia, splenic infarction, renal symptoms (especially gross or microscopic hematuria), severe pains, change in the color of the face, marked sternal tenderness, and emaciation. Blood-cultures should always be made in all cases of fever if the cause is not apparent. This is especially true if a valvular defect is present. Details of the methods of making such cultures do not form part of our topic today. I would, however, emphasize the following points. More than one blood-culture should be made if the earlier cultures are negative in results and the case is not clinically cleared up, the cultures should be made in optimum media, and all cultures should be observed for at least eight days. Blood-cultures are of no greater value in any condition than they are in the diagnosis of the disease the remarkable clinical features of which have today engrossed us.



## CLINIC OF DR. THOMAS F REILLY

### FORDHAM HOSPITAL

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#### THE MINOR AND MISLEADING EARLY SYMPTOMS OF DISEASE OF THE HEART AND CIRCULATION

PATIENT H. S , thirty-eight years of age (male), has suffered from weakness for the past year In the past two months he has had cough and expectoration During the past six months has averaged four night sweats each month, has lost about 6 pounds in weight, his appetite and digestion are good, he has trouble in getting to sleep, but after that sleeps well, frequently during the day he is drowsy and sleepy, after the night-sweats he feels very much depressed in the morning These sweats occur early in the morning and are most marked around the neck and limbs, chief complaints weakness, cough and expectoration, and night-sweats

The history thus far obtained sounds like a picture of what disease?

FIRST STUDENT Pulmonary tuberculosis

DR. REILLY Now we will go on to the physical examination He is a short, stocky man, well developed, no defects in the head or face, pulse is 80, regular, the vessel wall feels hard and is not easily compressed, the blood pressure is 220-125, rectal temperature  $98\frac{1}{16}^{\circ}$  F , respiration 20, no defects noted in the lungs, not even a single r le can be heard, the heart presents a systolic murmur at the apex and a diastolic murmur at the base, the blood is normal, negative Wassermann

Urine Specific gravity, 1010, trace of albumin, numerous hyaline and granular casts

The x ray shows the lungs to be absolutely normal and the heart enlarged to the left



Closer questioning now shows that he gets up at night to pass urine on an average of three times. He states that his wife complains that his breath is offensive most of the time. He has had bad taste in the mouth on arising more or less continuously for the past four months. It passes off after breakfast. Continued observation has shown that his temperature never goes above 99° F in the rectum. Many examinations fail to show T. B. in the sputa. After he had presented himself he was enjoined to rest for three hours daily, given kali iodid, 4 grains, and sodium bromid, 20 grains, three times a day to lessen the nervous irritability. The blood-pressure came down to 190 and remained there, meanwhile the sweats disappeared, cough ceased, bad breath and bad taste were not noticeable, and he felt well. Since then whenever he has had a hard day at business almost invariably he has a sweat at night, and for a day or two after has a bad taste. This is one group of cases that are frequently referred to a sanatorium or a country hotel because of supposed T. B. They go, and the rest and change, freedom from human care and worry lower the abnormal high blood-pressure to what is normal for that individual at that time, and lessen the concomitant symptoms.

On closer examination we see that this patient is suffering from cardiovascular renal disease, but the history is so strongly suggestive that the diagnosis of T. B. is very tempting. The night-sweats are particularly apt to lead one astray.

The recognition of disease is much the same as the recognition of a candidate for university honors. There must be two or three major and one minor requisite or one major and many minors. In medicine very frequently we have one major symptom and a whole group of minor symptoms that are just as valuable in aiding us to arrive at a diagnosis as would be the presence of several majors. No special skill is ordinarily necessary to detect major symptoms and signs, they write the diagnosis themselves, but the great fun and pleasure in medicine is the seeking out and the proper evaluation of the minor symptoms and signs. These minor symptoms constitute the early vanguard of disease and go stalking up and down in front of us constantly without recognition. As a matter of fact the profession does not need so much to be

shown new signs and symptoms of disease, as the repetition and reminding them of the well known signs and the evaluation of these minor symptoms of every-day life.

This is particularly true in such a system disease as cardiovascular renal disease. Among the common minor symptoms of this disease may be mentioned. Bad odor of the breath, more or less constantly present, bad taste in the mouth, particularly in the morning on arising, a dull suboccipital headache, an increase in the saliva, sleeplessness at night and drowsiness during the day, and weakness. Night-sweats are not so common, and because of their common association with T B are apt to lead us astray.

Sweating is one of the means of elimination in the body just as the urine and feces are. In some people the excess of poison which cannot be handled by the bowel and urine is eliminated by sweating or by the breath, and anything that interferes with the bowel or kidney elimination is apt to throw the burden on either of the other two. Sweating is, however, by no means always an eliminative process. In acute diseases the sweating of elimination is fairly common both day and night.

Here, for the most part, there is little difficulty in the diagnosis, the day- and night sweats of acute rheumatic fever, malaria, miliary fever, and sometimes of enteric fever are matters of everyday observation. The same thing happens to a less degree in the night-sweats of pyemia or pus collections. The night-sweats at the back of the head is such a common early symptom of rickets that it is almost diagnostic of the disease. Likewise the sweat that occurs with crises, collapse, antemortem sweats, coughing, and dyspnea are matters of daily observation.

The sweating of Graves' disease is not usually severe until the disease is self-evident. Here the frequent coexistence of T B with Graves' disease must be kept in mind.

In the last analysis the ultimate cause of most pathologic sweating, either day or night, is a toxic action on the sympathetic nervous system. The sweating of anger, rage, or that which follows section of the sympathetic are instances that demonstrate this. Occasionally the ultimate cause is due to an action on the greater vagus. In practice one meets with night-

sweats where the cause is not always clear at first sight in three types of cases

### 1 Hidden tuberculosis

2 A group of patients who present a syndrome mostly simulating the ordinary picture of neurasthemia, but differ in that they are more excitable, quicker in their actions than the ordinary neurasthenic. Frequently there is a previous history of night and day work, particularly mental in character. Generally it is possible to find a basic cause for this syndrome, and not a few of them have one or more major symptoms of *hyperthyroidism*.

### 3 Cases of cardiorenal disease

The diagnosis of the first group can commonly be made, provided a good history is taken and sufficient careful thermometric observations are employed. Indeed, any patient who has continued rise in temperature, lasting a month or more, with night-sweats and without any evident focal cause must be considered tubercular until proved otherwise. Here the night-sweats occur usually on consecutive nights.

The second group presents no elevation of temperature, are apparently well in every other respect, particularly as far as the organs are concerned. In these cases the sweats often have continued for months at a time without any evident bad effect. They react very well to sedatives and a few large doses of atropin.

In the cardiorenal cases the sweating only appears after some physical or mental stress which puts an added load on the kidney, thus compelling the skin to act vicariously. A nose cold, a digestive attack, or a long day's work are sufficient sometimes to cause a series of night-sweats. This patient is very well when he works seven hours a day, but if he does more work than that, particularly if he works in the evening, the night-sweat occurs. His business demands overwork on Thursday, and on that night he usually has a sweat. In these patients the sweating is not severe and is, for the most part, confined to the neck and limbs. It is very rare to meet with the drenching sweats of T. B. or of pyemia.

In the morning, however, the patient feels depressed and wakes just as though he had gone through some psychic shock. After a meal this passes off.

*The treatment may be summed up*

1 In rest, both mental and physical.

2 The use of sedatives, as 20 grains of bromids three times each day, sometimes combined with 5 grains of chloral.

*In stubborn cases* Atropin, gr  $\frac{1}{16}$  at bed time, is usually successful, but is not generally employed because of the disagreeable after-effects

Bathing of the body with vinegar and water (1 to 8 parts) is a home remedy, often efficacious

It will be seen that the course as well as the treatment of night-sweats in this group is much like that of the treatment of hyperthyroidism, and there is much evidence going to prove that they are closely related. Many of these patients have an abnormally wide ocular slit, have fine tremors, blush readily, and have other minor symptoms of dysthyroidism.

*Bad Breath*—When this occurs as a more or less constant phenomenon the individual grows accustomed to its presence, and, aside from his occasional noticing that people withdraw from the immediate radius of his face, no special attention is paid to it, and unless questioned directly he will not vouchsafe the information that it is present. It is commonly believed that bad breath is generally due to bad teeth, and all sorts of odorous tooth pastes are employed to nullify the odor. They do this for half an hour or more, but I believe the teeth, even though they look the part, are seldom the cause of bad breath.

By smelling the breath as it comes from the mouth with the nostrils closed one can at least rule out *sinus disease*. If the mouth be now closed and the breath coming from the nostrils is *still* foul, then the cause is likely to be below the throat.

In the course of pulmonary suppuration of any kind the breath is commonly very disagreeable.

Acute or chronic sinus disease is perhaps the most common cause of constant bad breath.

Sometimes tonsils whose crypts are filled with cheesy masses cause periodic spells of bad breath of which the patient is entirely unconscious. Chronic constipation or a septic gall bladder often

causes it There are numerous other causes, but they are generally evident on inspection

It is a fairly common symptom in the early stages of chronic renal disease before the onset of major symptoms

Bad breath is such a common every-day complaint that seldom is any attention paid to it It occurs occasionally in everyone, especially on the day following a heavy meal or after the ingestion of certain foods It is here an excretory function, is relieved by starvation or a purgative, and is commonly regarded as an evidence of gluttony, and thus dismissed with a smile

In some women it occurs during the menstrual menses, and is here also an evidence of excretion

In the presence of advanced chronic uremia it is almost always present It is quite impossible to describe the odor except that in the late stages it may be described as uriferous

In this patient it was present constantly for the past four months, but he noticed (or rather his wife noticed) it for weeks at a time previously, and then it disappeared His wife describes it as a heavy breath Finally, it may be stated that the presence of bad breath more or less constantly present without manifest disease of the air-passages warrants the search for a constitutional cause to find out why nature is excreting foreign substances through the air-passages, and of these constitutional causes *renal disease* is a very prominent one

*Bad Taste* — Closely associated with bad breath is the question of sensation of bad taste in the mouth, particularly on arising in the morning The complaint of occasional bad taste is such a common one after an indigestible meal that people are loath to complain of it It is, like bad breath, commonly relieved by fasting and a cathartic, but when it becomes a more or less constant fixture one must regard it seriously Here, again, I believe the teeth are not often to blame Roughly speaking, the laity are apt to blame the digestive tract as a cause of bad taste, whereas the profession is apt to charge it to the teeth After the use of a tooth-wash undoubtedly the taste is temporarily relieved or another substituted for it, but the effect does not last more than an hour or so Like bad breath, sinus disease, cryptic

tonsils, and pulmonary suppuration are occasional causes of bad taste, but in each of these the cause is self-evident and is easily explained, but when bad taste is frequently present in the absence of manifest local disease to explain it one must look for a systemic cause.

Of these systemic causes, none is more common nor persistent than diseases of the blood vessels or kidney. The taste is commonly described as an acid one, and is present in the morning on arising. It usually disappears during the day—once present, it is seldom absent for any interval. Sometimes it is described as a bitter taste, like that of black coffee. It is present as an early symptom in about half of the cases of chronic renal disease. It closely resembles and keeps pace with the suboccipital headache so characteristic of early nephritis. Very often it is increased by the ingestion of large quantities of proteins, particularly meat.

In this patient it is not constantly present, and bears a close relationship to his improvement or regression, as the case may be.

Drowsiness during the day is another symptom which is commonly ascribed to laziness, digestive troubles, etc. Most of the patients with renal disease, it is true, do not sleep well at night, and this would seem at first sight to account for the drowsiness during the day, but drowsiness during the day is frequently present in those who do sleep at night. One might theorize as to the cause of this drowsiness, but the fact remains that it is a fairly common early symptom in chronic vascular renal disease.

In this patient it is not a marked symptom, although at times it is annoying.

There is little to do for it from a medical standpoint.

Weakness is such a common complaint, especially among women, that it has little diagnostic import when considered alone as a presenting symptom. When it is severe, there are always other concomitant symptoms that should lead us to a correct diagnosis. Weakness in men usually means a serious lesion somewhere in the body. The most common errors arise in not seeing the exophthalmic goiter, anemia, primary or secondary, diabetes, tuberculosis, or nephritis that is present behind the screen. In women it is so commonly associated with the meno-

pause and the psychasthenias from whatever cause, that in the absence of manifest organic disease it spells bromids. Incidentally it may be remarked that one of the most common therapeutic errors of medicine is the current use of strychnin in such cases. Weakness is almost always present to some degree in the early stages of circulatory disease, whether it be cardiovascular or renal. Usually the patient must be questioned as to its presence, because it does not become manifest or troublesome until later. It must not be confused with dyspnea. The patient is simply more exhausted than formerly at the end of the day. He cannot do the work that he did some months previously. It is a valuable corroborative symptom. Once present, it seldom entirely disappears, but, on the other hand, is usually progressive. This is especially true in vascular and renal disease.

In this patient weakness is thus far not a prominent-symptom, but on questioning him one finds that he is not able to accomplish his former daily quota of work because he is so easily tired. Prolonged rest always temporarily relieves this symptom.

The second patient is a young lady, twenty-eight years of age, the family history is entirely negative except that both mother and grandmother suffered from frequent attacks of "*rheumatic fever*". Her own past history shows that she has never had any severe illness or accident. Six months ago she began to notice slight *dyspnea* and *husky voice*. At this time she was suffering from a severe attack of *bronchitis*—a disease which she had from time to time since infancy—cough was frequent with much expectoration, and at times blood streaked. Since then the dyspnea and husky voice have been marked at intervals. Three months ago during a coughing spell she expectorated a teacupful of blood. Since then on one or two occasions after running upstairs she has raised a teaspoonful of blood. After the hemorrhage she feels better. She has lost 7 pounds in weight in the past six months. When she has attacks of bronchitis there are slight rises in temperature, 101° F for three or four days, otherwise no fever is present. The chief complaints are weakness, dyspnea, hoarseness, cough, expectoration, and hemoptysis.

Thus far we have a fairly clear history of *tuberculosis of the teeth*.

The physical examination reveals a florid individual head normal. In the upper jaw there are two large central incisors about twice the size of the other teeth—tombstones.

The presence of these large teeth often suggests that the person is susceptible to the rheumatic micro-organism the net result of this being

- 1 Rheumatic fever
- 2 Endocarditis
- 3 Finally death and tombstones

This does not mean that everyone who has abnormally large upper central incisors will run that course, but from clinical experience it is always suggestive of a person likely to be attacked by rheumatic fever, and warrants a close inspection of the heart in such people.

The lungs are negative except for a few rales in the left posterior portion of the chest below the angle of the scapula. The pulse is regular, small, compressible, vessel walls not thickened, frequency 72, temperature 98° F, respiration 20, the sputa examinations made on several occasions were negative for '1'.

*Heart*—Presystolic murmur at the apex, snapping first sound; accentuated second pulmonic and a thrill, the apex in the fifth space within the nipple line.

The x ray examination shows the lungs to be entirely clear, the heart oval in shape, enlarged to the right.

The physical examination proves that we are dealing with a case of *mitral disease* (stenosis), and this will account for all of the symptoms.

STUDENT Can we not have also pulmonary tuberculosis present in this patient?

DR. REILLY Of course this is always possible, *there is no No or Neter in medicine*, but the absence of a slight constant elevation of temperature, no increase in the pulse rate, and finally no '1' after many examinations at least prevents a positive diagnosis of T B. Furthermore, active T B and mitral stenosis are not commonly associated—one reason being the damaging lack of



blood into the lungs that makes a poor culture-media because of the congestion

Clinical experience shows that there is some antagonism existing between true rheumatic fever and active tuberculosis, and while this is not an absolute antagonism, it is at least the rule. In this patient it is the pulmonary hemorrhage, hoarseness, and cough which is so likely to lead one astray, particularly during the short period wherein the temperature is slightly elevated.

The most common cause of hemoptysis is undoubtedly pulmonary tuberculosis, and it is responsible for approximately 95 per cent. of all hemoptysis met with in practice.

Mitral stenosis is the next most frequent cause, and represents about 3 per cent. of the cases.

Commonly in T. B. the hemorrhage comes on spontaneously. In mitral stenosis it usually comes on after severe coughing or exertion, and once the hemorrhage occurs, it frequently repeats on strenuous exertion.

In T. B. this is not the rule, but the sputa is streaked for a day or two following the hemorrhage.

When mitral stenosis causes hemorrhage there is not much difficulty in determining the presence of valvular disease.

In T. B. the patient is either greatly frightened at the presence of blood or is utterly callous as to its import, but he always feels weaker as a result of the hemorrhage.

In cardiac disease, on the other hand, the patient almost always feels better and is not so apt to be terrified by the presence of the blood.

SECOND STUDENT What is the cause of the mitral stenosis?

DR. REILLY This patient is quite positive that she has never had, to her recollection, either rheumatism, tonsillitis, or scarlet fever, the common causes of mitral stenosis. However, when we go back over the family history we find that her mother and grandmother suffered from rheumatic fever—this was the source of infection. The attack doubtless occurred in early infancy and did not attract attention. The infant cannot explain that it has so-called "growing pains."

In infancy and childhood the joints are not swollen. As a

rule there is present an elevation of temperature for a few days, a red throat, and endocarditis, the physical signs of which may not be evident until the doctor has ceased his visits, if he is called for the supposed "intestinal toxemia."

*Rheumatic fever* is just as contagious to young children as is *tuberculosis*. In the presence of an endocarditis in a child one can always find the history that someone else in that house had rheumatic fever or its direct descendant (*i. e.*, mitral disease), whether it be the parent, nurse, or old grandmother who fondles the child.

Heart disease, as such, is not inherited, but the early infection by rheumatic organism present in such patients is equivalent to the contraction of endocarditis.

Hoarseness is sometimes a symptom of mitral stenosis. It is then due to paresis or paralysis of the recurrent laryngeal nerve. This occurs because the nerve on the left side is squeezed between the left pulmonary artery and the aorta, a neuritis ensues, and is responsible for the paretic cord. In this case the hoarseness is usually associated with a tracheobronchitis, which, while it lasts longer than is usual, recovery of the voice ensues upon the resolution of the bronchitis, so that it cannot be considered as being due to recurrent nerve neuritis.

In this individual case rest in bed for two weeks and digitalis in small doses will affect a cure for the time being. The chief aim of treatment is the prevention of fresh attacks, proper occupation, no strenuous exercise (as dancing, etc.), avoidance of acute infections, such as cold in the head, etc., and, above all, eight hours of sleep each night. She may go on for a year or more without future attacks, but almost certainly future attacks will recur.



# CLINIC OF DR R G SNYDER

## CITY HOSPITAL

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### A DISCUSSION OF 3 UNUSUAL CASES OF ANEURYSM OF THORACIC AORTA, WITH AN ILLUSTRATED REPORT OF THE SUBSEQUENT AUTOPSY FINDINGS

#### CASE I

GENTLEMEN Our first case is a middle aged man, who was admitted to the City Hospital two weeks ago complaining of

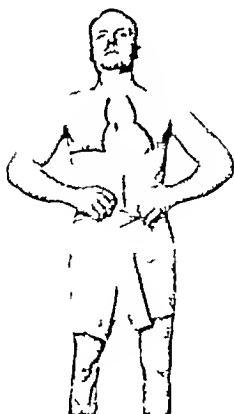


Fig 28.—Showing position of aneurysm and marked swelling of both arms

sudden swelling of the upper half of his body (Fig 28) This condition is associated with a slight amount of cyanosis and a

tendency to become dyspneic on slight exertion. He feels weak and often suffers from a dull pain in his chest.

The patient was a sailor until five years ago. Since that date he has been working in a wagon factory. He denies having had syphilis, but admits that his wife has had two miscarriages since the birth of the last child. The present illness started six months ago as a sudden sharp pain in his left chest. It came on while he was attempting to lift a heavy block of wood. During the following two weeks he was troubled so much with precordial pain and dyspnea that he was obliged to remain away from work. His condition gradually improved, but he did not feel strong enough to resume his former work, so he was given the position of night watchman.

On the day before his admission to the hospital he had a violent quarrel with his wife. At the height of the quarrel he experienced a sudden sharp pain in his left chest, followed by a sensation of suffocation. At the same time the members of his family noticed that his face, arms, and neck had become very dark in color. During the night he had great difficulty in breathing. He was admitted to the ward the following morning in practically the same condition as you see him, except that his face and trunk were more swollen at that time.

On physical examination one is immediately struck with the appearance of the patient, who shows an edema of the upper half of the body. The patient sits up in bed supported by four pillows, and says that he is unable to lie down for fear of smothering. His pupils are small, equal, and do not react to light and accommodation. The apex-beat is not visible or palpable. No abnormal pulsations are visible. Percussion showed cardiac and aortic outline as seen in the photograph of the patient. The radial pulse-rates are 110, regular, and they are approximately normal in character. A definite tracheal tug is present. Over the aortic area there is a loud systolic murmur, which is transmitted to the vessels of the neck. In addition to this there is a second murmur which is difficult to describe. This particular murmur has been the subject of a great deal of discussion among the various attending physicians and the interns of the hospital.

Some of the men believe it to be a very long diastolic murmur. They think that they can detect a short interval between its termination and the beginning of the systolic murmur already described. Others believe it to be one continuous murmur, with systolic exacerbation at the aortic area. The systolic part of this murmur is accompanied by a pronounced rough vibratory thrill which is palpable over the upper part of the sternum. The thrill and murmur could be heard and felt in the vessels of the neck on both sides when he entered the hospital. At present these can no longer be detected on the left side of the neck and it should be noted that the edema and cyanosis are now more noticeable on the left arm. The aortic second sound is present, but somewhat diminished in character. Wassermann reaction is positive and temperature, respiration, and lung signs are approximately normal.

**Discussion.**—Mr. A, in your opinion what are the most probable possibilities in this case?

**ANSWER 1** Aneurysm of the ascending portion of the aorta plus pressure on the superior vena cava.

**2** Aneurysm involving the ascending portion of the aorta plus perforation into the superior vena cava.

**3** Rupture or tearing of the aortic cusp.

**QUESTION** Mr. B please give us the evidence for and against the diagnosis of an aortic arch aneurysm plus pressure on the superior vena cava.

**ANSWER** The percussion outline, the tracheal tug, the constant cough and difficulty in swallowing, with a suspicious syphilitic history (stiff pupils in a sailor whose wife had had two successive miscarriages after the birth of healthy children), and positive Wassermann reaction all point very strongly toward the diagnosis of an aneurysm involving the first and second portions of the aorta. If this murmur is a double aortic murmur it would agree very nicely with the diagnosis of an aneurysm of the first portion of the arch, as these murmurs are usually associated with a widening of the aortic ring and a resulting aortic regurgitation. We may assume that the first sudden pain, following the lifting of a heavy weight, was coincident with the original break in a dis-

cased aortic wall, and caused the beginning of the aneurysm. To explain on this contention the subsequent cyanosis and edema coming on suddenly six months later is somewhat more difficult. To cause cyanosis and edema of the head, neck, and both



Fig. 29—Photograph showing the heart and aneurysm after the anterior third of each has been removed. The long piece of paper indicates the normal course of the aorta, while the short piece of paper is placed through the perforation from the aorta into the superior vena cava. On the upper surface of the aneurysm can be seen the remains of the left innominate vein, which was completely thrombosed.

arms it would be necessary to obstruct the return flow of venous blood from these areas. It is conceivable that the aneurysm is pressing on the superior vena cava in this case, but the probabilities are much against it, because it would be very difficult for an aneurysm of the first or second portion of the aorta to obstruct

the superior vena cava, as the latter is normally situated at a considerable distance posterior to the aorta in this particular location

QUESTION Mr C, what do you think are the possibilities of this being a case of an aneurysm of the aorta, with a perforation into the superior vena cava?

ANSWER Although I have never seen such a case and I understand they are very rare, it would seem to be the more probable



Fig. 30.—Rear view of the aneurysm and heart, showing the superior vena cava emptying into the left auricle and at the upper end of the superior vena cava can be seen the perforation which was the cause of the murmur and cyanosis.

diagnosis, if it could be established that the murmur is continuous in character and that its variation is simply due to a systolic exacerbation. The acceptance of this theory would satisfactorily explain the following sequence of affairs

1 A sudden sharp pain in the chest which was so severe that the patient was obliged to give up work for two weeks, and then



accept a position which required no physical exertion. We could assume that the pain was due to a tear or partial break in the aortic wall, which was presumably already diseased in a man suffering from syphilis.

2 The aneurysm apparently slowly enlarged without causing much trouble when the sudden increase in blood-pressure caused



Fig 31 —Picture of thorax immediately after the median incision had been made, and the pericardium dissected away to show the relationship of the aneurysm to the heart and to the superior vena cava

it to rupture into the adjacent superior vena cava. That would explain the sudden cyanosis and swelling of the upper half of the body, associated with a rough thrill and continuous murmur which could be heard in the large arteries on both sides of the neck.

3 The disappearance of the thrill and murmur from the left

side of the neck can be accounted for by a further upward enlargement of the aneurysm, causing a total occlusion of the left innominate vein

4 The slight cyanosis can be interpreted as being due to the mixing of the arterial blood with the venous blood



Fig. 32.—Photograph of the chest taken while the patient was still on the autopsy table. The aneurysmal sac has been pulled away from the superior vena cava. At the upper left-hand corner it will be seen that it was adherent to the superior vena cava just below its division into the two innominate veins.

QUESTION Mr D, what are the possibilities of this case being due to a rupture of the aortic valve?

ANSWER The attack of sudden sharp pain, followed by cardiac embarrassment, would make it necessary, of course, to rule out this possibility. This diagnosis can be quickly eliminated

by the absence of water-hammer pulse, the comparatively slight enlargement of the heart, and the impossibility of explaining the edema and cyanosis of the upper half of the body on this contention

**Summary** —Although at first some of us were in doubt as to the character of this murmur, the majority of the staff have decided in favor of the diagnosis of an aneurysm of the aorta with perforation of the superior vena cava, as this is practically the only condition which would account for the presence of a continuous murmur and thrill as well as a sudden appearance of cyanosis of the upper half of the body

*Note* —The 3 cases included in this clinic were shown to the students of the College of Physicians and Surgeons, and at a later date I was able to show them the autopsy specimens. In order to enable the reader to visualize the clinical report and the autopsy findings I am inserting the pictures of the pathologic specimens immediately subsequent to the report of the case

**Clinical and Pathologic Summary** —This case evidently suffered from unsuspected syphilis. It finally attacked his aortic arch so that it was weakened to such an extent that it could not stand the rapid increase in aortic pressure secondary to the effort of lifting a heavy weight. By changing the character of his work the patient was able to compensate temporarily for the presence of the aneurysm. However, the sudden fit of anger caused a weak spot in the aneurysmal sac to give way. Luckily for the patient it burst into a vein. He eventually died from a cardiac failure

## CASE II

Negro, aged fifty-five, who was admitted to the hospital complaining of dyspnea on exertion and more or less constant precordial pain. He said that he had never been ill, with the exception of having had a chancre twenty years ago. During the past two months he has experienced difficulty in swallowing food. He is also troubled with occasional bad metallic cough, and at times he brings up a moderate amount of mucopurulent expectoration. This has never been observed to be blood tinged. The total duration of the present symptoms has been six months, and they have

~~was~~ gradually progressive in character. The following is a short ~~summary~~ of his physical examination. The patient is a well pre-~~sent~~ middle-aged negro, who lies in bed supported by two ~~staves~~. His temperature is  $98.8^{\circ}\text{F}$ , his respiration 22, and pulse 110. The pupils are equal and active. There is no palpable ~~evidence~~ of glandular enlargement or visible evidence of venous ~~enlargement~~. A distinct tracheal tug is present. In percussing ~~over~~ the upper border of the heart one can distinguish an abnormal area of dulness into the second and third interspaces on the ~~right~~ side, extending  $2\frac{1}{2}$  inches from the midsternal line. Over this ~~area~~ there is a visible and palpable pulsation, but no thrill or ~~murmur~~. The heart is evidently slightly displaced downward to the left, and is otherwise negative. The systolic blood pressure in the right arm is 120, in the left 130. The aortic second sound is not markedly accentuated. The pulse-rate is 110, otherwise normal in character. Over the left lung posteriorly the breath sounds are somewhat more distinct in character, and inspiration is accompanied by numerous moist râles. The liver is palpable 1 inch below the costal margin. There is no edema of the feet. The reflexes are apparently normal.

Discussion — QUESTION Mr A., what are the most probable possibilities to be considered in discussing this case?

ANSWER 1 Aneurysm involving the transverse portion of the aorta.

2 Mediastinal tumor

3 Mitral stenosis with extreme distention of the right auricle and an associated auricular fibrillation

QUESTION Mr B., what evidence have we for and against the diagnosis of aneurysm?

ANSWER 1 The persistent and increasing precordial pain

2 The visible pulsation and abnormal area of dulness to the left of the upper part of the sternum.

3 A positive tracheal tug, associated with a hard, *brassy* cough, and difficulty in swallowing

Negative — 1 *The absence of any type of heart murmur*

2 The absence of diastolic shock.

3 The equality of the pupils

4 The very slight difference in the blood-pressure of the two arms

QUESTION Mr C, will you give evidence for and against the diagnosis of mediastinal tumor?

ANSWER The symptoms and physical signs which are produced as a result of pressure from an aneurysm could be equally well produced by the pressure of a tumor. These would include the cough, difficulty in swallowing, and pain. We must admit that the tracheal tug could be the result either of an aneurysm or of a mediastinal tumor pressing upon, or becoming adherent to, the left bronchus. The pulsation might be regarded as the normal pulsation of a moderately large transverse arch from the aorta through the medium of a tumor, but the most important evidence in favor of the diagnosis of mediastinal tumor is the definite absence of a cardiac murmur, as an aneurysm of the first portion of the aorta is almost invariably associated with aortic regurgitation. However, the regular outline of the abnormal area of dulness, the lack of emaciation, and of glandular enlargement are very strong evidences against the diagnosis of tumor.

QUESTION Mr D, what do you think is the possibility of this case being due to some cardiac disease other than that of aneurysm?

ANSWER In view of the fact that there is no marked evidence of venous engorgement, such as edema of the feet, a pulsating liver, and marked distention of the veins of the neck, it is much more plausible to consider that the slight outward and downward displacement of the heart is due to downward pressure of an aortic arch aneurysm or mediastinal tumor. In addition to these facts, there is a total absence of cardiac murmurs. Absence of cardiac murmurs occasionally occurs in cases of mitral stenosis which are associated with auricular fibrillation and extreme distention of the right heart. It is true that they often show a moderate increase in the area of dulness to the left of the sternum in the third interspace, due to the engorgement of the left auricle, but even in these cases the dulness would hardly correspond with the area just described, and they are invariably

associated with great distention of the veins of the neck, which is not true of this case

**Summary**—In view of the fact that aneurysms involving the first and second portions of the aorta are comparatively com

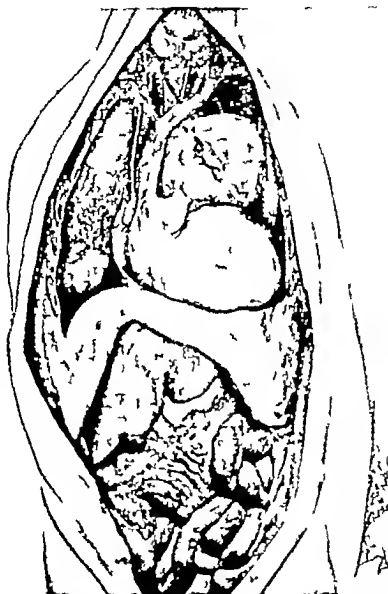


Fig 33—Sacculated aneurysm of the first part of the aorta. The pericardium was adherent over the upper part of the sac. The aneurysm pressed on and collapsed the left lung and it also involved the left recurrent laryngeal and phrenic nerves

mon, it is probably wise to assume that the patient under discussion is suffering from this disease especially as he has a positive specific history. It must be admitted that a positive diagnosis cannot be made between aneurysm and tumor in this case. But

in this connection it must be remembered that Cabot, in studying a large series of autopsy records at the Boston City Hospital, found that three-fourths of the cases diagnosed at that hospital as mediastinal tumor proved to be cases of aneurysm. We shall, therefore, leave our diagnosis as an unproved but suspected aneurysm of the aorta.

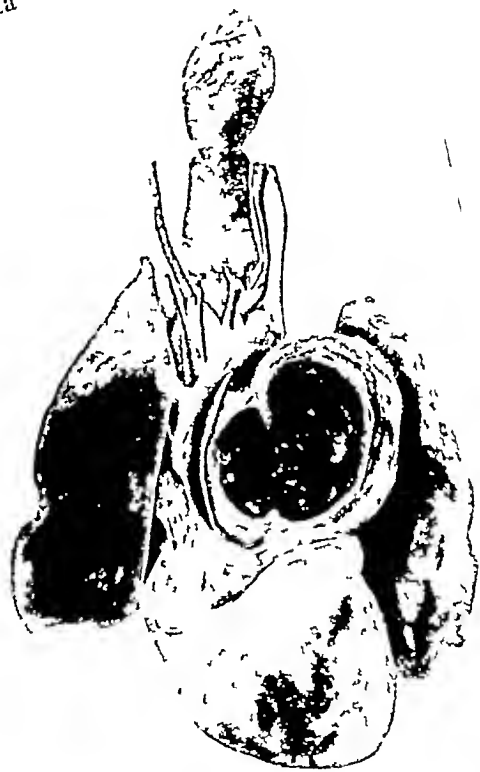


Fig. 34—Aneurysm of the first part of the aorta cut in section, showing its communication with the aorta and its interior filled with laminated blood-clots.

**Autopsy Report**—Figure 33 is a picture taken with the camera elevated 4 feet above the autopsy table. A median incision has been made, and the anterior portion of the thorax has been removed, as well as the anterior layer of the pericardium, in order to expose the heart and large blood-vessels. The heart is dis-

placed downward and to the left by a tumor which is about the size of a medium sized orange. The left recurrent laryngeal nerve is adherent to and embedded in the wall of the tumor.

Figure 34 shows an enlarged view of the heart and its relation to the tumor and the lungs. The anterior third of the tumor and of the aorta has been removed, showing that the tumor consisted of an aneurysmal sac projecting from the left side of the ascending aorta. The sac was completely filled with an organized blood clot, so that the aneurysm had all the physical characteristics of a solid tumor.

It is therefore easy to see why it was impossible to differentiate between the conditions during life.

### CASE III

**Introduction** —I shall first give you a short account of the history and physical examination of the patient as taken from the chart on the day of admission to the hospital. I wish you to follow it carefully, as I intend to ask you to examine this patient and state whether you agree with the original diagnosis which was made four days ago.

J. K., admitted to the hospital complaining of pain in left upper chest, which was increased on deep inspiration. Duration two days. He had had scarlet fever during childhood and gonorrheal infection four different times. The last occurred six years ago. He has had several attacks of rheumatism. The first occurred ten years ago after exposure to wet and cold. It was characterized by sudden onset of swelling of the knees and ankles. Duration four days. He had a second short attack four years ago, and each winter subsequent to that date. Only the ankles and knees have been involved up to the present. He denies specific infection and says that he has never had pain in the chest or any cardiac respiratory symptoms. Two weeks before entrance to the hospital the patient had a sudden attack of acute inflammation in the elbow, which later extended to his shoulders. This attack lasted ten days. The day before admission the patient was taken with severe and sudden pain in the left chest, and this was increased by deep inspiration. It was accompanied



by moderate dyspnea and expectoration of bloody mucus. The patient is an adult white man about sixty years old, lying in bed, complaining of pain in the left chest on deep inspiration, although he does not appear acutely ill. The pupils are equal, regular, and react to light and accommodation. The left upper lobe apparently shows complete consolidation. There



Fig. 35 —Admitted to the ward as case of pneumonia, involving the left upper lobe

is dulness on percussion. Breathing is bronchial in type with prolongation of expiration, and at the end of inspiration many fine and coarse crackling râles may be heard. Percussion causes severe pain in the left upper chest. The heart is apparently not enlarged, the sounds are distant and obscured by the lung sounds. No murmurs are audible. Pulse is 110 and regular. Abdomen, glands, and extremities negative. Knee-jerks present.

and equal The temperature is 102° F Respiration 30 Leukocyte count is 17,600 Polymorphonuclears 81 per cent.  $\alpha$  Ray shows apparent complete consolidation of the left chest A provisional diagnosis of lobar pneumonia was made by the



Fig 36— $\alpha$  Ray plate taken on the day of admission.

intern staff and was confirmed by myself and one of my colleagues

Discussion.—QUESTION Mr A, will you kindly examine this man and tell us what you find in regard to his condition today, and

whether you agree with the provisional diagnosis of lobar pneumonia?

REPLY The patient seems to feel fairly comfortable and is not coughing much. He says that he can lie on his left side, which he could not do before on account of the severe pain. There is still tenderness to percussion over the left upper lobe anteriorly and the percussion note seems to be particularly flat in this region. Bronchial breathing can be plainly heard over the entire left upper lobe, but not over the lower lobe. Over the left base one can hear many coarse and fine moist crackling râles both anteriorly and posteriorly. On consulting the chart I see that the temperature is 101° F. Respiration 24 to 28. Pulse 90 to 100. The leukocyte count is 20,800. Polymorphonuclears 81 per cent. I also note that the left knee-joint is swollen, red, and tender. It apparently contains fluid and has been aspirated. The laboratory report shows that although the fluid obtained contains many pus-cells, the smears and culture were negative. I should think that the patient is at present suffering from a lobar pneumonia involving the left upper lobe. The lower lobe is in a stage of resolution. It is probable that he also has a pneumococcal infection of his knee-joint.

DR SNYDER I have taken the trouble to show this case to impress upon you the importance of a careful and thorough physical examination, and also to impress upon you the fact that you must observe your patients carefully and conscientiously from day to day. You must remember that none of you will ever reach the stage of perfection in physical diagnosis or medical reasoning that will justify you in assuming an air of overconfidence in your diagnostic ability. The day following this patient's admission it was noted that the percussion note over the upper left chest was somewhat peculiar in that it was flat, whereas that over the rest of the chest was dull. A needle was inserted into the second interspace about 2½ inches from the midsternal line with the expectation of finding fluid, but with negative results. It was observed that his temperature was of moderately low type, varying between 100° and 102° F, and that his inspiration although it occasionally went to 28 to 30, for the most part re-

mained between 22 to 26 per minute. Another careful physical examination brought out two very important physical signs. The patient had a very distinct and easily palpable tracheal tug and a subacute prostatitis and seminal vesiculitis. We therefore,



Fig 37—Autopsy picture showing heart aorta left lung and the position of the large clot which conducted the bronchial breathing to the anterior chest wall.

in all probability, have to deal with a large transverse arch aneurysm which is associated with some type of secondary pulmonary consolidation. It is evidently not of tuberculous origin because repeated sputum examinations have been made and are negative for tubercle bacilli. Very frequently the partial compression of

the bronchus causes a retention of bronchial secretions, and this seems to serve as a starting-point for a peribronchial pneumonic consolidation. The fact that this patient has had attacks of sharp excruciating pain in this area associated with the expectoration of bloody mucus would lead one to conclude that the consolidation was intimately connected with hemorrhages into the bronchi as a result of erosion of the bronchus by the aneurysm. We still have to explain the temperature and joint symptoms. In this connection I wish you to recollect that he has had four different attacks of gonorrhea, and that the first attack of rheumatism occurred previous to his last attack of gonorrhea. He is now suffering from a subacute prostatitis, and in the absence of any other known source of infection (especially as the heart valves have not been involved and the fluid taken from the knee-joint showed negative cultures) it is probably most reasonable to assume that the patient is suffering from a coincident gonorrheal arthritis.

**Subsequent History**—The patient died suddenly at a later date, apparently as a result of a large hemorrhage into the bronchi, as he expectorated a great quantity of bright blood.

**Autopsy Report**—This shows that the patient was suffering from a moderately large aneurysm involving the transverse and the first portion of the descending aorta. On the anterior surface of the aorta at about the junction of the transverse and descending portions was a perforation about  $\frac{1}{2}$  inch in diameter. This evidently occurred at the time the patient had the first sudden sharp pain in his left upper chest two days before his admission to the hospital. The patient was saved from sudden death at that time by the fact that the lung had previously become firmly adherent to the aneurysmal sac, to the adjacent pericardium, and to the anterior chest wall. In spite of these adhesions a sufficient amount of blood was forced through the opening to form a large thrombosed clot about the size of a man's hand over the left lobe. The clot had formed a solid medium which had transmitted the bronchial breathing from the bronchus to the chest wall. On the posterior and inferior surfaces the aneurysm had been gradually corroding the left bronchus, and the gradual oozing or weeping of blood from this area had caused

the expectoration of bloody mucus. The collection of blood in the alveolar air-cells had helped to produce the deceptive x-ray picture. As a terminal event the aneurysm had burst into the left bronchus, flooding the left lung with blood.

Before closing I wish to express my appreciation to Dr Harlow Brooks and Dr Charles Quinby for the use of the first and second cases respectively, and to Dr John Larkin for the use of the autopsy material.



# CLINIC OF DR. WALTER JAMES HELMANN

## POST GRADUATE MEDICAL SCHOOL

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### THE RELATION OF INTERNAL DISTURBANCES TO DERMATOLOGIC CONDITIONS<sup>1</sup>

Intimate Correlation of Dermatoses with Constitutional Disturbances. False Conceptions of Cutaneous Medicine Essential Features of Dermatoses as a Whole Types of Acquired Dermatoses, Numerous Combinations of Manifestations and Many Clinical Variations Besnier's Doctrine of Skin Reactions Broad Principles Guiding Modern Interpretation of Etiologic Factors. Skin Manifestations in Metabolic, Gastro-Intestinal, Excretory, Vascular, Blood, Central Nervous System, Endocrinal System, and Body Chemistry Disturbances. Focal Infections Cases Illustrating Eccentric Behavior of Psoriasis Following Dietetic Therapy Rational Basis of Skin Phenomena.

In recent years, and particularly in America, an attempt has been made to correlate many of the so-called cutaneous diseases with internal and general medical disturbances. The expression "so-called cutaneous diseases" has been employed advisedly, because the feeling is growing that many of the dermatoses formerly considered clinical entities are merely syndromes. In this sense it is important for the general practitioner to realize that a working knowledge of dermatology may lead to the recognition of general disturbances that would otherwise escape his attention, and it is important for the dermatologist to realize that he, in turn, should stop regarding dermatology as a narrow specialty and view it rather with the eyes of an internist.

<sup>1</sup> Clinical lecture on dermatology delivered June 4, 1918 at the Post-Graduate Medical School.



In reviewing the modern history of dermatology it becomes apparent that a system of inadequate language has been built up side by side with a science. Numerous conditions closely related, because of superficial distinctions, have actually been regarded as dissociated clinical entities. This has resulted in a confusion, if not chaos, in our concepts of cutaneous medicine, and it is likely that it will take a century before dermatology can be reinterpreted in terms of contemporaneous medicine. It must not be assumed that because dawn has risen in the east of the dermatologic night that the passage of the sun will be unretarded, but it is safe to say that it is only through readjustment of dermatology to the laws of morbid biology that we can ever aspire to a high noon in this branch of medicine. The faintly lighted horizon gives some encouragement.

Before endeavoring to point out what the relationship is between dermatology and general medicine it will be necessary to discuss some of the essential features of dermatoses as a whole. In order to do this it would be wiser to restrict the topic under discussion to acquired dermatoses of which the causation is not definitely known. This eliminates all congenital malformations, tumors, and infections of the skin. The conditions remaining may be roughly classed in the following groups: urticaria, dermatitis, the scaling skin diseases, the lichens, and the vesiculobullous eruptions.

It must be remembered that the skin is a tissue enveloping many other organs and tissues. It must further be remembered that there can be no great independence of the skin from the rest of the body, for if there were, the skin would not react as it does in the acute exanthemata for example. As soon as this is admitted, the bridge has been crossed which dermatology has to traverse to be included in the rational branches of medicine.

If the skin is slightly inflamed, it gets red. If the inflammation continues, the skin swells. If the inflammation is still further sustained, there is a tendency to chronic changes. Most dermatoses are inflammatory, and in understanding this the dermatologist becomes a gross pathologist with special reference to the integument. Inflammation in the skin, as anywhere else,



responses Arsenic is able to cause herpes, hyperpigmentation, hyperkeratosis, simple dermatitis, and erythemas resembling the exanthemata Iodids and bromids may cause toxic erythema, chronic granulomas, varicella-like eruptions, a certain form of acne, and the like This indicates the fact that in different people a given poison provokes different types of response, varying according to the susceptibility and power of resistance of the individual It is unnecessary to carry the examples further in order to clarify the subject matter under discussion, for if the principles here involved are broadly applied it will indicate the possible relations and dissociations of causes and effects in the production of what we are pleased to call skin diseases

All diseases that are not due to anomalies of development, new growths, and pure mechanical influences represent an effort on the part of the body to resist a poison Nor does it make any difference whether this poison is created within the body or introduced into it from without Whether it is the result of metabolic disturbances or whether it is the result of infection, whether it is due to functional derangement of the various systems of organs or of the glands of internal secretion or the vegetative nervous system as a whole, the militant factor in disease must be an abnormal substance within the body, however it gets there, and the symptoms of the disease are always an expression of the effort of the body in some way or other to overcome or expel the intruder In the last analysis disease is always a process indicating a biochemic disturbance At times the body response is so characteristic or the cause so well known that the disease becomes a clinical entity More often, and particularly in dermatology, so far as we know, this is not the case The symptoms of disease are largely subjective, but in cutaneous conditions the range of symptoms is not great, and hence they are of clinically little importance On the other hand, the objective signs of disease, namely, the lesions themselves, are of great variety in cutaneous medicine and, consequently, of great importance In internal medicine, because we cannot see the lesions while the patient happily remains alive, the study of symptomatology is more important than that of lesions to the clinician In

dermatology, since the lesions are exposed to anyone's view, the clinical science of this branch of medicine has tended to become objective

It is unnecessary to discuss in greater detail the technical aspects of skin lesions. In order to grasp the thesis here being developed it makes very little difference whether you know all of the meticulous distinctions that define the several skin lesions. But it is necessary always to remember, and therefore the matter is advisedly emphasized here, that countless causes may provoke one type of skin lesion, and that several types of skin lesion may be provoked by one cause. The agents provoking cutaneous responses may be found outside of the body or inside of the body. It is more especially with the latter that the present lecture concerns itself.

We must further subdivide internal causes of skin responses into those probably found in the alimentary tract, the excretory system of the body, the cardiovascular system, the hematopoietic system, the central nervous system, and the vegetative nervous system including the glands of internal secretion. In addition to this, it is essential to remember that disturbances of the body chemistry, without any necessarily ascertainable organic changes, play a most important rôle in the causation of dermatoses. At this point it is necessary to recall that any such artificial separation of the enumerated systems from one another and from their respective functions is quite as unphilosophic as it was to build up a system of dermatology without reference to all the other organs in the body. The entire body is a physiologic as well as an anatomic unit. On the whole, it must always be remembered that even though the main expressions of a disease may apparently be referable to one system of organs, the process itself may actually exist in an entirely different system, as, for example, the tachycardia and tremor of Graves' disease, the essential process of which resides in the thyroid gland. Thus we may not logically attempt, particularly at the beginning, to say such and such a group of skin diseases represents an alimentary disturbance and another a renal disturbance, and so on. The matter, in all

branches of medicine, is more complicated, and no more so in dermatology than in the rest

With these broad principles in mind let us examine what little may be surmised regarding the internal causes of dermatoses. It will perhaps prove to be very little, and still that little is considerably more than would be possible if we adhered to the dogma of the early schools. With the profoundest reverence for the service that Hebra rendered to the science of dermatology, it is nevertheless a fact that he was largely a visual dermatologist. Probably no other worker in his field has had such acute eyes as this venerable Viennese scholar. The real tragedy in the history of the subject was Hebra's ability to out-thunder the teaching of Willan, the father of modern dermatology, who beheld the subject more clearly than any of his successors for a century. It is only within the last decade or so that it has again become possible to realize how superior was the attitude of the English school. Advances in modern medicine will enable us again to take up the thread of the work that was interrupted one hundred years ago at Willan's death.

Numerous cutaneous manifestations are referable to alimentary disturbance. Rosacea, seborrhea, and acne vulgaris are among them. In rosacea we often find an associated chronic gastritis, sometimes gastric ulcer, very frequently hyperacidity, and carbohydrate indigestion. Chronic alcoholism and the extensive use of tea and coffee, probably through their effect on the stomach, are also frequently the underlying factor in rosacea. The proof of this lies in the fact that the skin manifestations diminish or disappear when the underlying cause is controlled. In women, certain pelvic disturbances, particularly in connection with the menses and menopause, appear to bear a causal relation to rosacea. How this is to be reconciled with the gastric disturbances it is hard to state unless it be through the intermediary of the endocrinous system. Chronic enterocolitis, particularly when due to carbohydrate fermentation, also causes rosacea. Seborrhea in all of its forms is not only frequently associated with rosacea itself, but also with any and all of the underlying causes of rosacea.

The form of dermatitis known as eczema which is due to an ~~acquired~~ <sup>acquired</sup> outside cause is very frequently associated with chronic constipation, protein putrefaction and vitamin deficiencies. This is also the case in the chronic urticarias, such as prurigo, and not infrequently in dermatitis herpetiformis. Associated with this phenomenon and in these conditions, particularly with the last two, nitrogen retention occurs constantly or periodically. Thus a second group of cutaneous reactions can be realized which is more or less consistently related to disturbances of protein digestion and nitrogen metabolism. Here again the therapeutic test is of corroborative value for cases of this type, treated not only locally, but with cathartics, eliminatives, and intestinal irrigation, run a shorter course than with local treatment alone.

A feeling seems to exist, based upon inferences published by Bulkley and the really scientific work done by Schamberg, that psoriasis is also the result of a disturbance in nitrogen metabolism, but this is not entirely clear. Psoriasis is most capricious; it comes and goes as it chooses without relation to the habits, life, or diet of the patient. It sometimes gets better and sometimes worse during pregnancy, lactation, or menstruation. It even varies in this respect in the same individual. It gets better

or worse during chronic cachectic or acute diseases. It manifests itself equally on a protein or a vegetable diet. An eminent dermatologist in New York, intending to impress his audience with his acumen, said to a new patient who presented herself at his clinic for treatment for psoriasis, "Stop eating meat and eggs." This was his first interview with the patient and he had taken no history. Her reply was "I never tasted either in my life."

Another case comes to my mind of a woman with a universal psoriasis who, having been put on a rice diet, developed a generalized erythroderma and a mucous colitis, with acid stools and a marked starch indigestion. When put on a mixed vegetable and protein diet, with no other local treatment than vaselin, her skin cleared up in two weeks.

Still another case. A young matron, immediately after having lost 20 pounds in weight, developed a recrudescence of her psoriasis, a fact which is markedly at variance with Schamberg's findings. This loss in weight was not due to ill health, but to an energetic out-of-door existence following a sedentary winter. As a matter of fact, although we know nothing of the cause of psoriasis, it is as easy to find arguments against its origin in disturbed nitrogen metabolism as to find arguments for it.

The relation of dermatoses to excretory disturbances is, so far as our present knowledge goes, slight. Sometimes in chronic nephritis, with or without nitrogen retention, there is itching of the skin and sometimes vesicles or papular eruptions of the eczema or prurigo type are observed. Considering, however, how common nephritis is and how infrequent its association with these conditions, one must look further when they coexist instead of blaming the skin condition on the kidney condition. It is far more likely that the two are individual, although associated expressions of a common underlying cause. Chronic nephritis is, in the main, the result of a sustained intoxication which at the end of years and by means of its effect on the general circulation, both anatomic and physiologic, leads to morbid changes in the kidney. In some instances there may be gangrene of the skin, but this can in nowise be

ascribed directly to the renal changes. As a matter of fact, it is a local circulatory change that precedes the dermatosis.

This brings us face to face with the relation of cardiovascular and simple vascular changes to skin diseases. Inflammations of the arteries, whatever their original cause, when the nutrition of the skin is disturbed are capable of producing such gangrene as one sees in leg ulcers, Raynaud's disease, scleroderma, perforating ulcers, decubitus, chilblains, and the like, and in each one of these conditions the immediate cause is a vascular disturbance. This vascular disturbance, however, may be due to vasomotor, mechanical, or toxic causes. In cardiovascular disturbances, when through early decompensation the excretion of the body is disturbed, such dermatoses may arise as are due to disturbed nitrogen metabolism. This, in turn, refers us back to the relation of the kidney to the skin. Unquestionably, an extensive skin disturbance throws an added excretory burden on the kidneys and vice versa, and thus, although it is probable that as time goes we will recognize more cutaneous conditions dependent upon the cardiovascular renal system, at present we can only get an inkling of the fact.

Similar cutaneous changes, such as those summed up under the rubrics of *purpura annularis telangiectoides*, *angioma serpiginosum*, *dermatitis hæmostatica*, and Schamberg's progressive pigmentary disease, are referable to anatomic changes in the skin vessels. These changes lead to a dilatation of the vessels, purpura, pigmentation, and atrophy, with or without frank gangrene. What the underlying causes of the vessel changes are we do not know, but a brilliant light has been thrown on the matter in Stokes' excellent paper on syphilitic telangiectasia. Reasoning backward from this, it is possible to infer that in the final analysis the underlying factor in all of these conditions is a toxin with a peculiar affinity for the cutaneous vessels. I recall a patient in my service at the Lenox Hill Hospital, a man fifty years of age, with an extensive dermatitis on what was apparently a seborrheal basis. All conventional treatment for this condition had been in vain. A positive Wassermann reaction necessitated his being treated for syphilis. With his first mer-



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cury injection his itching stopped and he very promptly improved. A microscopic examination of his skin showed an extensive endarteritis such as one sees in syphilis. Although seborrheal dermatitis is not included among the syphilids, it is probable that the vascular changes in this man, caused by his syphilis, provoked a skin reaction which appeared to be seborrheal dermatitis, and with the rapid improvement of his cutaneous vessels the dermatitis cleared up. How far-reaching an inference may be drawn from an instance of this sort it is not safe to state, but it amply proves that classic names clear up *no* mysteries.

Disturbances of the blood, as such, outside of the leukemias, cause very few alterations in the skin. One may practically exclude the primary anemias, so far as we know today, as causes or associated phenomena of cutaneous changes. The leukemias may produce scaling and favor itching spots on the skin of any type, of course beautifully labelled in dog Latin or dog Greek, small itching papules or more voluminous tumors. Closely related to these are the cutaneous changes of Hodgkin's disease, and a condition called mycosis or, better, granuloma fungoides. All of these conditions start more or less insidiously with a prodromal dermatosis resembling psoriasis, scaling eczema, parapsoriasis, or urticaria, that may last for months or years before the papules or tumors appear. There is reason to believe that these conditions are primarily also related to skin sarcomatosis. The entire subject is still rather vague. Sometimes persistent itching papules or even vesicles suggesting dermatitis herpetiformis may be the first indication of leukemia, and a differential blood count will reveal the diagnosis. In another instance every indication will point to leukemia, and the leukocyte count prove to be normal. We satisfy ourselves by regarding such cases as aleukemic leukemia. The practical point to remember is that many itching dermatoses are the result of leukemia, and therefore it is necessary to rule out this possibility when the suspicion arises.

Diseases of the central nervous system cause a great number of skin changes, and it will be impossible to enumerate them

all in this brief space Suffice it to say that probably there is no immediate connection between the central nervous system and the skin, but there is some remoter connecting link. In other words, it is the influence of the central nervous system through the means of the vasomotor and sympathetic mechanism that produces the skin alterations. In this sense many of the diseases described in the paragraph on vascular disturbances may be referable to the central nervous system, or the last may influence the skin trophically and produce functional changes which, in turn, determine anatomic alterations. Thus the central nervous system in a great many instances is responsible for various gangrenes, acro-asphyxia, erythromelalgia, Raynaud's disease, scleroderma, and allied conditions. In this connection it is well to emphasize that mental diseases in a peculiar manner may produce dermatoses. People of abnormally low intelligence or of hysteric habitus inflict injuries upon themselves to provoke sympathy or puzzle their medical attendants. These cutaneous phenomena, though obviously not of central nervous origin, at least indicate mental obliquity which the astute observer may detect by careful interpretation of skin phenomena. Recklinghausen's disease, granulosus rubra nasi, and many nevi have been described as associated with congenital mental deficiency. It is important here to rule out the element of coincidence inasmuch as the skin disturbances very much more often occur without such psychic phenomena.

Disturbances of sweat secretion, partial or total baldness of certain types, and zoster have all been proved in many instances to be the result of central nervous disease or of injuries to the central nervous system. Zoster particularly is associated with hemorrhages into the anterior horns. Kreibich, of Prague, published a classical monograph on the subject of angioneurotic edema in which he proved experimentally that blebs or blisters could be produced on the skin under hypnosis. It is certainly true that herpes genitalis often occurs in psychopathic individuals after illicit sexual congress. I recall one case in which simply pointing out this fact to a victim of chronic genital herpes produced a cure.

The relation of skin diseases to disturbances of internal secretion is in its infancy precisely to the extent that our knowledge of the physiology of the endocrine system as a whole is. It is unnecessary to repeat to practitioners that in Graves' disease and cretinism there are certain well-known changes in the skin and its appendages which may be cured by thyroid therapy. The literature is replete with statements to the effect that the administration of thyroid and pituitary extract cure or improve many dermatoses. Particular emphasis has been laid on the value of pituitary extract in scleroderma, and although it has proved valuable in some cases that I have seen, I have never myself treated a patient successfully for this condition by this or any other means. Nevertheless, considering the reliable source of some of the statements, pituitary extract should be given as a routine measure in scleroderma after thyroid therapy has been attempted.

It is possible that the subtler phases of disturbed carbohydrate metabolism registered by an increase in the sugar content of the blood may be referable to the thyroid gland or the pituitary body. If this is so, the conditions dealt with in the paragraph on acne, seborrhea, etc., might be beneficially influenced by proper therapy with extracts from the ductless glands mentioned. One dermatologist in New York treats all his cases of acne with small doses of thyroid extract. My own experience in this respect has not been gratifying except in one case in which very small doses of the substance combined with strychnin were prescribed. The use of pituitary extract in excessive hairiness, particularly in fat young women of the masculine type, has a logical basis, but when practically applied I, personally, have not found it useful. Nevertheless, there is enough truth and enough scientific foundation in the entire matter to warrant further efforts tempered with optimistic skepticism and restraint. The disappointments that are experienced in using ductless gland extracts are perhaps due to the undeveloped state of the science of endocrinology as a whole, and it is not fair to swing from irrational extravagance to equally irrational mockery of these therapeutic agents.

In this connection it might be well to refer particularly to the use of suprarenal extract in dermatology. In cases due to known or presumed disturbances of the suprarenal glands, such as Addison's disease and various other pigmentary disturbances, the administration has been of no use. On the other hand, in anaphylactic phenomena of the skin, such as urticaria and angioneurotic edema, the substance is often valuable. I have seen at least half a dozen patients with chronic urticaria relieved and two of them cured, and at least a dozen cases of acute urticaria cured with from two to five injections of suprarenal extract. In one patient with angioneurotic edema of the upper eyelid the symptoms were immediately controlled by instilling a drop or two of the extract in his conjunctival sac, and subsequently it was possible to prevent further recurrence by determining, by means of percutaneous tests, the particular protein which caused his disease.

Disturbances of body chemistry as a whole, partially independent and partially referable to the foregoing, have a bearing on skin diseases. Thus, as already stated, disturbed nitrogen and sugar metabolism are often at fault. Without repeating anything that has already been said, it is necessary for a moment to refer to diabetes in its relation to the skin. The diabetic may suffer with ordinary evanescent dermatitis, intertrigo, furunculosis, and skin gangrene. It is impossible to state whether it is the sugar itself or the underlying cause of the diabetes that produces the skin changes, but at least in gangrene the alterations are due to vascular disturbances and in furunculosis the condition may be due to the excess of sugar in the blood, precisely as in acne and rosacea. Disturbance of sugar metabolism is certainly at the root of xanthoma diabeti-corum, while disturbance of fat metabolism is responsible for xanthoma tuberosum. There is this difference between the two, however the latter is incurable and the former disappears when the sugar leaves the urine. This indicates that an increased knowledge of human biochemistry will undoubtedly throw light upon other dermatoses still considered etiologically obscure.

The relation of allergy and general sensitization to the pro-

duction of skin disease is a fascinating subject still in its infancy. Aside from the problems of sensitization that play a rôle in infectious disease there appears to be a substantial group of cutaneous reactions depending upon local sensitization of the skin, or general sensitization of the body with skin responses, provoked by alien proteins. It is with the latter group that we are more concerned. Unquestionably, urticaria and prurigo and probably some forms of eczema and possibly dermatitis herpetiformis may be so caused. The test in each instance would depend upon discovery either by eliminating offending proteins or by determining their pathologic relationship to the disease by percutaneous tests in the sense of von Pirquet. The experiments of Schloss in connection with egg, walnut, and almond urticaria blazed the trail in this country at least. Proteins have been isolated from all the common food-stuffs, a good many flowers, and from the hairs of many domestic animals. Unquestionably, their causal relationship to some of the conditions mentioned has been established. In the hands of the scientifically and judiciously disposed this method of determining etiology will prove of great practical value. There is danger though in the misuse and misinterpretation of these reactions on the part of enthusiasts who constantly look for medical toys to play with in a pseudoscientific spirit, or who regard every new biologic test as a milestone on the royal road to diagnosis which is ordinarily paved, not like the path to Hades with good intentions, but with mental indolence. All of these new discoveries will not make medicine easier, but harder, because more complicated, and percutaneous tests with various proteins unless properly read, studied, and classified will not clear up, but will confuse our concepts of disease causation. In a case recently studied this method of diagnosis proved to be of great value. The patient, already cited in an earlier passage, was a man with angioneurotic edema of the left upper eyelid which upon close observation was found to recur suddenly after midnight on a given day in the week. He had been for years in the habit of having buckwheat cakes for supper on this day. He responded percutaneously to buckwheat with a very marked

reaction, and elimination of this food caused the disappearance of the disease. Examples of this sort are multiplying in the literature, and probably we may ultimately find this diagnostic method of as great value in dermatology as Cooke has found it in hay fever. I must be forgiven for concealing my scientific enthusiasm in this field under great conservatism, for I do not think the time yet ripe for statements that may in the future be interpreted as jejune.

Another phase of the relation of internal medicine to dermatology is embraced in the now popular medical tango of focal infection. Undoubtedly the *Streptococcus viridans* and other streptococci tucked away in a tooth abscess or a tonsil or even an appendix may and do produce far-reaching results in the joints and heart valves, and they may unquestionably and unquestionably do produce some skin reactions. But the pendulum has swung too far. They do not and cannot explain every cutaneous disease, from the pimple on a young girl's chin to a prickle-celled cancer, as some of the protagonists maintain. At the last meeting of the American Medical Association it was stated by one of the speakers that he had seen, in two patients, dermatitis herpetiformis disappear after some offending teeth had been extracted. This is not to be doubted. On the other hand, I myself have seen a case of dermatitis herpetiformis for the first time make its appearance after similar dentistry. Then, again, I recall a patient who had what was clinically pityriasis rubra of Hebra. He was told by his physician, in the rôle of Job's comforter, that he would positively die very soon. In order to make his last days comfortable he had his teeth drawn. In two weeks his skin was normal and the man is living now, five years later, perfectly well. Cases of urticaria, prurigo, erythema multiforme, and erythema nodosum have improved after the removal of infectious foci. Other cases have not. On general principles it is to be urged that when an abscess exists in the human body it ought to be removed, and if certain incidental, far-flung symptoms then disappear we may reasonably infer that the abscess caused the symptoms. We are not yet, however, in a position to argue



backward, and we cannot tell when given phenomena are produced by a focal infection. Nor does it always follow that when the removal of a focus of infection is succeeded by a disappearance of symptoms, that we may place the blame for the latter upon the former. The most difficult thing the human mind has to combat is *post hoc ergo propter hoc* reasoning. With all due respect to the important rôle played by focal infection in the etiology of dermatoses, it is nevertheless desirable to be cautious about the exclusive adoption of the latest medical waif that appeals to our hearts rather than to our minds.

This, then, represents a survey of the few facts and hypotheses that exist in connection with the relationship of internal medicine to abnormal skin phenomena. It is hard to predict precisely whether the paths indicated will lead anywhere, but it is certainly necessary constantly to try to explain skin phenomena on the basis of rational medicine, and to put an end to the arbitrary isolation that dermatology has maintained in clinical medicine. The skin participates in disease processes and does not possess a series of processes peculiar to itself. It will be the duty of future dermatologists with the viewpoint of internists to work out the details of the relationship of dermatology to internal medicine.

CONTRIBUTION BY DR. MURRAY H. BASS

NEW YORK

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## THE CUTANEOUS MANIFESTATIONS OF ACUTE RHEUMATIC FEVER IN CHILDHOOD<sup>1</sup>

Diagnostic Importance of these Cutaneous Manifestations in Childhood   List of Common Lesions   Case of Simultaneous Rheumatic Erythema and Chorea. Erythema Nodosum of Rheumatic Origin, Illustrative Case   Purpura Rheumatica with Report of Case. Types of Rheumatic Erythema. Dermatoses with Rheumatic Submillary Nodules in Heart Muscle. Report of Case of Erythema Multiforme with Aschoff Cells Demonstrated at Autopsy   Consideration of Aschoff Bodies and Their Significance in the Diagnosis of Rheumatism. Conclusions

THE cutaneous manifestations of acute rheumatic fever are more commonly met with in childhood than in adult life, and are of considerable importance from the standpoint of diagnosis. The lesions may be grouped under the head of erythema, urticaria, purpura, and edema. Considerable confusion exists in regard to these lesions, since each one of them is merely a symptomatic expression of the action of the rheumatic poison on the skin. It must, therefore, be clearly understood that any of these lesions may appear in the course of other diseases where they are the result of toxins other than the rheumatic. In other words, we may have erythema or urticaria in children who are not in any way suffering from rheumatism. The same skin lesions, however, so often make their appearance in conjunction with typically rheumatic symptoms that one is forced to include them among the clinical manifestations of acute rheumatic fever.

<sup>1</sup> Based on a Demonstration of Cases and Specimens before the Pediatric Section of the New York Academy of Medicine, May 9 1918.

Quite recently, moreover, histologic studies have tended to confirm the above-mentioned relationship between skin lesions and rheumatism in the study of the so-called "rheumatic nodule" of the skin and the submiliary nodules in the heart muscle, for there appear to be certain elements of resemblance between the microscopic appearance of these two structures, to which Coombs and others have called attention. This similarity of structure is certainly suggestive and is well worth further investigation.

Not only is this similarity of lesion demonstrable, but I am fortunate in being able to present a case of marked erythema marginatum accompanying acute rheumatic carditis in which postmortem examination revealed submiliary nodules in the heart. In spite, therefore, of any arguments to the contrary, there can be little doubt that certain skin lesions should be regarded as manifestations of acute rheumatic fever, and in the following pages will be found several cases of rheumatic infection in which the cutaneous lesions were of importance.

CASE I—Seymour B., aged three, was brought to the Mount Sinai Dispensary in May, 1917, on account of an eruption of the skin. At the age of a year and a half he had measles. He had frequently suffered from sore throat. The eruption appeared a few days before his visit to the dispensary, and spread over the back and extremities, accompanied by slight itching. There was no history of digestive disturbance, and the bowels had been regular. There was no history of drug ingestion. The mother stated that the child had had slight fever. He had never before had any skin eruption.

Physical examination showed a fairly well-nourished, pale boy, with a temperature of 101° F. On the extremities and buttocks there was an eruption of many discrete, violaceous, shiny, raised, hard, flat maculopapules varying in size from a grape-seed to a dime. The eruption was most profuse on the extensor surfaces about the knees and elbows, and especially so over the buttocks (Fig 38). The tonsils were hypertrophied and congested, but there was no exudate. Otherwise the physical examination was negative.

On account of the identical type of eruption and the same

distribution seen a few weeks before in an adult suffering from acute rheumatic arthritis and endocarditis, the diagnosis of rheumatic erythema was made and salicylates were prescribed. In spite of the medication, however, three days later the child developed chorea and one week later mitral endocarditis.



Fig 38—Erythema papulatum (Case I) showing distribution and character of lesions. Boy aged three years suffering from chorea and mitral endocarditis.

In July 1917 a tonsillectomy was performed, following which the boy though retaining a mild mitral insufficiency, was apparently in good health until April 1 1918. On that day he again appeared at the dispensary because of a simultaneous recurrence of the eruption and chorea. The mother stated that a few days

previously the boy had complained of pains in his feet and had become irritable and feverish. The eruption was identical with that observed one year before, both as to its character and its distribution. The exhibition of salicylates and rest in bed seemed to improve the condition temporarily.

On July 3, 1918, the boy was seen again, with chorea much more marked, and with a very profuse crop of lesions of the erythema papulatum type, as before noted. The heart lesion was apparently unaffected by the therapeutic measures taken, and was evidenced by a loud blowing apical systolic murmur transmitted to the axilla, accompanied by signs of enlargement.

To recapitulate. A boy of three, previously well, reveals an eruption of erythema papulatum, accompanied by slight fever. One week later he develops chorea, and a few days after that mitral endocarditis. Under appropriate treatment the chorea and the skin lesions disappear and the child shows no acute symptoms for a period of a year, when the chorea and erythema again appear simultaneously.

Another type of cutaneous lesion concerning whose relationship to acute rheumatic fever much has been written is erythema nodosum. Although there is much in favor of the view that erythema nodosum is a specific disease entity, there are so many instances reported of its association with other rheumatic symptoms that I believe one is forced to conclude that at times this cutaneous manifestation must be due to the rheumatic toxin. True, it is met with less often than the other erythemata, but, as Cheadle says, "Its appearance, from time to time, in immediate connection with the rheumatic outburst seems to stamp it as one of the rheumatic phenomena, and it is occasionally met with in childhood."

I have reported such a case where a child aged two and one-half years developed pharyngitis, torticollis, orchitis, and erythema nodosum,<sup>1</sup> all of them evidently "rheumatic" in origin.

The lesion of erythema nodosum is a shiny, bluish-red, raised nodule, often tender and hot to the touch. It is situated

<sup>1</sup> Jour Amer Med Assoc, May 24, 1913, lx

commonly on the anterior surface of the lower extremities, may be quite painful, and persists for two to three weeks. The individual lesion varies from 1 to 5 cm. in diameter and is circular or oval in outline and tense to the touch. As pointed out by Sutton, it becomes soft and fluctuating as it regresses, and can then be mistaken for an abscess.

Evidently very closely related to this typical clinical picture is that shown by the case next to be reported.

CASE II — Sybil S., aged four and a half years, was brought to the dispensary with a history of frequent sore throat and joint pains. The mother stated that the child had had several attacks of great pain in the arm and in the leg, accompanied by swelling of the affected extremity. There was fever with each attack, and each was said to last a few days and then subside, after which the child was apparently well.

Physical examination showed enlarged, diseased tonsils. There was slight tenderness over one ankle joint. The temperature was normal.

The mother was advised to have the tonsils removed as soon as the acute condition subsided. Two days later she brought the child again, who had now developed one of the attacks. The child looked very sick, temperature was 101° F., the pulse rapid. Over the left tibia there was a swelling involving more than half the length of the leg, exquisitely tender, hot, tense and the skin over it was shiny. At first glance the condition had the appearance of a neglected case of acute osteomyelitis of the tibia. The ankle- and knee joints were the seat of mild arthritis. The tonsils were still markedly inflamed. A radiogram was taken, but the plate showed perfectly normal bone. The Wassermann reaction was negative. Evidently we were dealing with a skin lesion very similar to an enormous erythema nodosum nodule. That this was the case was proved by the appearance two days later of a similar swelling over the right upper arm. The heat and tenderness were just as intense.

Under salicylates the disease cleared up in two days. The child has had her tonsils removed and, to my knowledge, has had no attack since then, now three months.

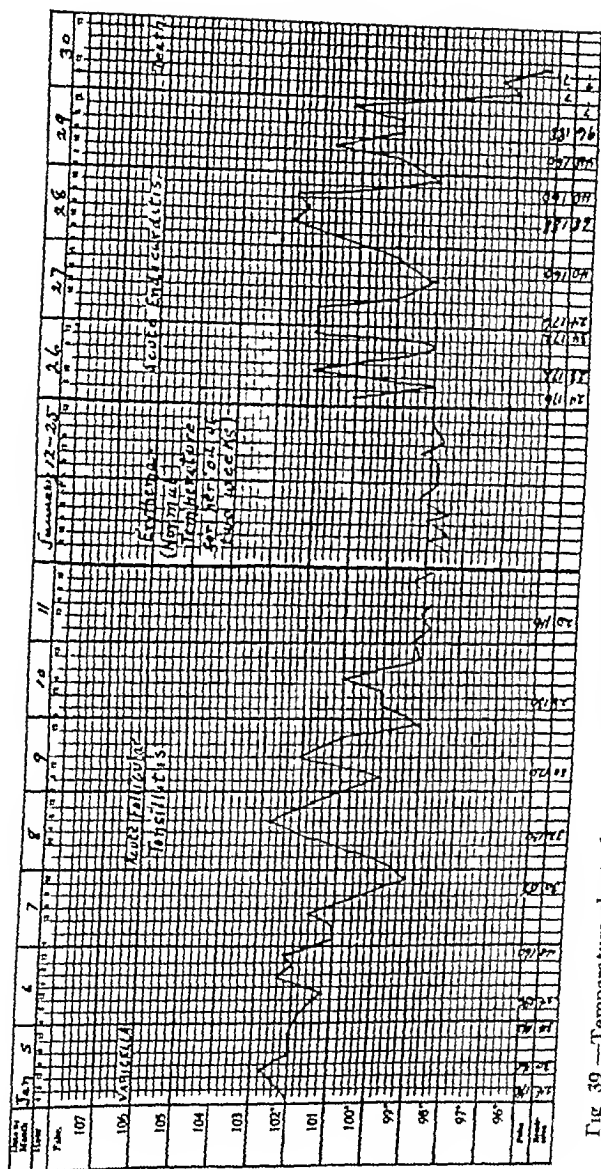


Fig. 39.—Temperature chart of Case II showing progression of illness. Mild varicella on January 5th, severe acute follicular tonsillitis on January 8th, two weeks of normal temperature, during which time an eruption of erythema marginatum made its appearance, culminating acute endocarditis on January 26th, with death five days later.

This case is of unusual interest since the type of eruption described is unique, and I have found only one similar case reported, that of a large, inflammatory, symmetric, cutaneous exu-

date in a girl of fifteen, suffering from recurring sore throat and arthritis<sup>1</sup>

A purpuric eruption is at times associated with acute rheumatic fever. As a cutaneous manifestation of the disease it is more common in childhood than among adults. It usually appears during the acute stage, the lesions often being profuse on the skin over the inflamed joints. Much confusion, unfortunately, still exists in regard to these eruptions. Some of the cases are undoubtedly hemophilia, the joint symptoms possibly being due to hemarthrosis, others are simple purpura, others are extreme forms of erythema, and still others are associated with bleeding into the intestinal tract, with severe cramp-like abdominal pains. In spite of this array of clinical pictures there is apparently a small group of cases which may be classed correctly as "purpura rheumatica." How confusing the separation of these disease entities is the following case will illustrate.

CASE III.—A little girl, aged six, was seen with severe abdominal pain of one day's duration, accompanied by vomiting and constipation. Examination revealed a tense abdomen, generally tender, temperature of 101° F., angina without exudate, a slightly swollen and tender left ankle-joint, and a vaginitis of gonococcal origin. The question arose as to whether the child had a gonococcal arthritis and a possible peritonitis. The finding of a few petechial spots over the affected ankle influenced us to wait before finally diagnosing an acute peritonitis, since purpura with abdominal symptoms could not fully be excluded. The following day we were justified in having temporized, for a profuse hemorrhagic eruption appeared over both ankles and knees and the stools became bloody. The case, therefore, was one of Henoch's purpura and the gonococcal vaginitis had evidently nothing to do with its etiology. To call such cases rheumatic is obviously stretching the term too far, yet there are all gradations from the above picture to simple tonsillitis followed by arthritis and purpura.

Probably the most commonly encountered eruptions of rheumatic origin are those included in the term "erythema." Ery-

<sup>1</sup> Riebold. Deutsch. Arch. Klin. Med., 1904-05 lxxvii.



thema marginatum, erythema papulatum, erythema exudativum, erythema multiforme, etc., are all terms used in describing varieties of this skin lesion. Some of them, as was mentioned above, gradually merge into the purpuras, others are associated with pruritis and in form resemble urticaria, while still others, accompanied by swelling, are grouped with angioneurotic edema. Osler long ago recognized this complicated relationship in his description of cases of visceral manifestations in patients showing lesions belonging to the erythema group. The close relationship of the various types of lesion and their dependence on acute rheumatic fever as a cause is emphasized by Oscar M. Schloss,<sup>1</sup> who described 4 cases, synopses of which follow.

*Case I* —Rheumatic fever, purpura, urticaria, angioneurotic edema, erythema simplex. Recovery.

*Case II* —Rheumatic fever, erythema nodosum, purpura, urticaria, erythema exudativum, intestinal hemorrhage, pericarditis. Death on the twenty-first day of the disease.

*Case III* —Follicular tonsillitis, erythema multiforme, urticaria, colic. Recovery.

*Case IV* —Tonsillitis, urticaria, erythema nodosum, period of improvement with the occurrence of angioneurotic edema. Sudden onset of pericarditis. Death.

In reviewing the above cases, one cannot help being impressed by the fact that all of these various dermatoses are interchangeable and that they all evidently depend on the same causative factor. Moreover, in the two fatal cases we have complications referable to the heart. This is of great importance in view of the next case I have to report, for although Schloss' cases are clinically to be classified as rheumatism, there is no definite pathologic proof of their being such. The following case, therefore, is of extreme interest, since rheumatic submiliary nodules in the heart muscle definitely stamp the case as one of acute rheumatism.

*CASE IV* —Florence B., aged three, was admitted to the Home for Hebrew Infants, on the service of Dr. Alfred Hess, on December 3, 1917. Previous and family history were unknown. Physical examination on admission was completely negative. One month later the child had a mild attack of vari-

<sup>1</sup> Amer Jour Med Sci, cxl, 1910

cella, followed five days later by a severe follicular tonsillitis and cervical adenitis. There was no evidence of joint involvement. Examination of the heart was negative. One week later, January 15th, a very pronounced eruption made its appearance over both elbows, knees, buttocks and, less profusely, on the back. The eruption consisted of raised, dark bluish red, somewhat shiny, smooth areas, circular or circinate in outline, and of various sizes up to that of a 25-cent piece. These efflorescences remained for about three days and then faded. They were unaccompanied by fever, but the child looked sicker than before and was kept in bed. Examination of the heart at this time was negative. After a period of one week, during which the child appeared to recuperate, the temperature on January 26th rose to 101° F. The child became paler and very irritable, and examination of the heart revealed a double murmur over the mitral area. For four days the temperature varied between normal and 102.8° F, the pallor and dyspnea rapidly increasing. Signs of cardiac dilatation appeared, with bilateral hydrothorax and puffiness of the face. In spite of vigorous medication the child died of cardiac failure four days after the discovery of heart involvement. There were no petechiæ at any time, no evidence of embolism, the spleen was never palpable, and the urine was negative. A blood-culture was ordered, but the child died before the blood was obtained.

To sum up, then, we have here a child of three years who had a severe tonsillitis, followed after one week by an eruption of erythema multiforme, and one week later by endocarditis, with death from heart failure after four days.

An autopsy was performed and the chief findings follow.

*Lungs* showed marked congestion. Bilateral hydrothorax, with clear straw-colored fluid.

*Liver and spleen* showed great congestion, the former being enormously enlarged, the latter very slightly.

*Pericardial sac* contained about 30 c.c. of straw-colored fluid.

*Heart*—This was examined for me by Dr. W. Thalhimer, and I quote his report verbatim.

"The heart is slightly larger than normal. Epicardial sur-

face is slightly roughened and shaggy. Right heart is slightly hypertrophied. Right auricle is otherwise normal. Tricuspid orifice is slightly dilated, and scattered irregularly along the edge of closure of the valve are small groups of glistening verruci. Pulmonary cusps show a very slight degree of thickening along their line of closure, but no verruci. Left auricle is considerably enlarged and its wall hypertrophied. Mitral valve shows along the line of closure of the flaps a wart-like vegetative process which extends downward upon the chordæ tendineæ. This vegetative process, however, is glistening and pinkish in color, and has not the appearance of a vegetative endocarditis, but has the appearance of a massive rheumatic verrucous endocarditis. These vegetations are large enough to have slightly narrowed the mitral orifice. The flaps themselves are slightly thickened. Left ventricle is markedly enlarged, its wall hypertrophied to one and one-half times normal thickness. The aortic cusps show along their line of closure a continuous line of minute beaded glistening verruci. The foramen ovale is closed. The ductus arteriosus is not present on the specimen. The aorta is normal in appearance.

*"Microscopic*—Hematoxylin and eosin stain. The muscle-fibers of the heart throughout are normal in appearance. Great numbers of typical Aschoff bodies are present throughout the section, situated in the interstitial tissue and also around the blood-vessels in the adventia (Fig 40). All of these bodies are made up of groups of Aschoff cells close to one another, separated, however, at the center of the group by pink staining, granular material. These cells are polymorphous in shape, some of them elongated. Their protoplasm, dense and very finely granular, takes a peculiar stain, being pink with slight purplish tint. The nuclei are relatively large and vesicular and many of the cells contain several nuclei. These Aschoff cells are readily distinguished from fibroblasts, although at the periphery of the group the cells shade off into the connective tissue of the adventitia. In the midst of the Aschoff bodies is an occasional plasma cell and large mononuclear leukocyte. Some of the Aschoff bodies contain thirty to forty cells. In none of

the Aschoff bodies is there any evidence of fibrosis Gram-Weigert stain failed to show bacteria either in the heart muscle or in the thrombus on the mitral valve "

The clinical course of this case was so rapid and the infection so virulent that bacterial endocarditis (*s. c.*, so-called malignant endocarditis) was suspected The autopsy findings, however, disposed of this diagnosis and absolutely proved the rheumatic origin of the disease

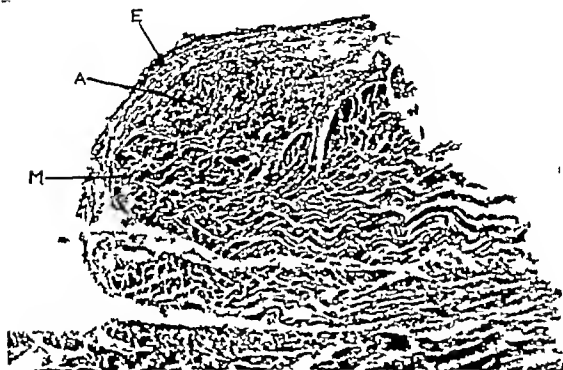


Fig 40 —Section of left ventricle of Case IV showing submiliary nodule or "Aschoff body" (A) endocardium (E) myocardium (M)

Though there is no strictly pathognomonic clinical sign or symptom of acute rheumatic fever, we do possess definite data concerning its pathologic anatomy The lesions found in the heart, as above described are characteristic The endocarditis is of a special type, always verrucous when fresh The lesions consist of small, firm, grayish pink, wart like nodules situated on opposing surfaces of the valves along the line of closure. "On section bacteria have rarely been demonstrable, and then in very small numbers, the only organisms found in the sections

or in culture (the latter more infrequently) were streptococci" (Libman)

Besides the endocardial involvement, however, very characteristic changes may be found in the myocardium, in the form of microscopic foci, forming submiliary nodules. These structures, first described by Aschoff and now known as Aschoff bodies, consist of aggregations of large cells scattered throughout the myocardium, mainly in the subendothelial portion, in the course of the medium-sized and smaller blood-vessels. The cells, according to their discoverer, are of connective-tissue origin, and with them are mingled lymphocytes and eosinophilic leukocytes. The nodules are most commonly found in the musculature of the left ventricle.

Aschoff says, "The nodules are found only in cases of positive, or very probable, rheumatic infection, but they are not always demonstrable, since they develop into tiny microscopic, scarcely recognizable perivascular scars. Occasionally parenchymatous-interstitial foci are present besides the specific nodule formation, but these rarely reach any considerable size."

These lesions have been very carefully studied by Thalhimer and Rothschild, whose conclusions follow: "In rheumatic myocarditis foci termed 'submiliary nodules of Aschoff' are present which are characteristic of rheumatic infection. They are most frequently found in the walls of the left ventricle, the auricle usually escaping. The nodules were found in 3 cases of chorea without joint manifestations, proving the close relation of this condition to rheumatism. They were absent in 14 cases of subacute bacterial endocarditis due to the *Streptococcus mitis*. They were not found in infections of the endocardium with the gonococcus, staphylococcus, streptococcus, or pneumococcus. Even in the absence of a rheumatic history we believe, in accordance with Frankel, that the presence of Aschoff bodies signifies a previous rheumatic infection. Aschoff bodies are not always found in rheumatic carditis where the affection antedates death by a long period, but the healed remains, represented by sclerotic patches, are present. We suggest that the cases of arthritis characterized by the presence of the sub-

miliary nodules of Aschoff in the myocardium be placed in one group and called, for the time being, 'rheumatism,' and the cases with articular manifestations, yielding positive bacterial findings and no Aschoff bodies, should be classified according to the infecting micro-organisms concerned, and not as rheumatism."

Carey Coombs has also very carefully described these lesions, and he points out that they are associated with the active phases of cardiac rheumatism, and are probably always present in such cases. He believes that the nodules are inflammatory and almost certainly infective in origin. "Their absence from other forms of carditis, and their likeness to the changes seen in other rheumatic lesions, make it possible that they are specific for the rheumatic form of carditis"<sup>1</sup>

In this condition the so-called rheumatic nodule of the skin is of interest. Strange to say, this particular cutaneous manifestation of rheumatism is but rarely encountered in America, whereas it is one of the common findings in England. These nodules are uncommon in adults, but not at all rare in early life. They may appear with any of the rheumatic symptoms, but most often accompany cardiac involvement. They are found beneath the skin, may be single, though usually multiple, and vary in size from a nodule barely perceptible to the touch to that of an almond. They may be quite evanescent, or remain for months. They are rarely tender. Their significance is not only diagnostic, but prognostic, since, as Cheadle says, "in the acute rheumatic fever of children when the nodules are many and large they have an ominous association with progressive endocarditis and pericarditis of the most serious kind, they indicate a grave danger, a carditis which is uncontrollable, and advances almost invariably to a fatal termination."

In the foregoing pages I have shown that in children various cutaneous lesions may make their appearance accompanied by, or as precursors of, rheumatic symptoms, have described illustrative cases of purpuric eruptions and erythema of various types, including a child in whom each of two attacks of chorea

<sup>1</sup> Jour. Bact. and Path., 1910-11 xv

was accompanied by a profuse eruption of erythema papulatum, have reported in detail the clinical and postmortem findings in a child aged five years in whom an eruption of erythema marginatum was followed after a few days by hyperacute carditis and death. The finding of submiliary nodules in the heart of this case made the diagnosis of rheumatism positive. These cases, I believe, will aid in the classification of these skin lesions and contribute a few further facts toward the establishment of the clinical picture of acute rheumatic fever. Case IV, with its postmortem findings, is particularly important as an additional proof in this connection, justifying the following conclusions reached by Osler: "The relation of the rheumatic poison to the arthritis and the other lesions is clear enough in some cases, but we cannot say that the arthritis is a hallmark by which we can always recognize the rheumatic poison. A great many of the cases of arthritic purpura or the peliosis rheumatica have, I believe, nothing to do with the poison of rheumatism. On the other hand, erythema, with or without purpura and arthritis, may be in children, as are endocarditis, tonsillitis, and subcutaneous fibrous nodules, manifestations of the rheumatic poison—links in the rheumatic chain."

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### ACETONE BODY ACIDOSIS IN CHILDREN

Acetonuria Versus Acidosis    Acetone Body Production. Effect of Excessive Production of Such Bodies. Directions for Estimating their Significance and Degree    Significance in Obscure Infectious Diseases    Acute Toxic Conditions in Young Children. Cases Illustrating Group in which Increased Acetone Body Production is an Expression of Toxemia, Clinical, Blood, and Urine Findings, and Relation of Average Excretion of Acetone Bodies to Body Weight. Prognosis    Principal Clinical Characteristics. Etiology    Treatment. Summary of Features of Importance

ACETONE bodies commonly occur in the urine of sick infants and children, and their occurrence is generally without clinical importance. It was believed at one time that acetonuria was synonymous with acidosis, and, unfortunately, like all such errors, the death of this idea has been slow.

Howland and Marriott have recently discussed the significance of acetone body production in infants and children. They emphasize that from our present knowledge the only harmful effect of increased ketone production is the possibility of it requiring sufficient alkali for neutralization to cause harm.

It requires a considerable quantity of acetone to form diacetic acid, and beta hydroxybutyric acid. In the alkali reserve of the body fluids, and with the increased production, or diminished excretion of acetone bodies which commonly occurs in children, is without clinical importance. As pointed out by Howland and Marriott the test used most



frequently for the detection of acetone bodies is the nitroprussid test for acetone, which is an extremely delicate one. The use of such a sensitive test has led to considerable error, as the small amount of acetone bodies excreted in many diseases (fever, starvation) has led to the assumption that acidosis was present.

An estimate of the significance and degree of acetone body production should be based on a quantitative determination of these substances excreted in the urine and present in the blood. The harmful influence of these substances can be determined by estimating the degree of acidosis produced.

Another feature which has tended to exaggerate the importance of acetone body production is the fact that in partial starvation considerable amounts of acetone may appear in the urine (nitroprussid test). In many obscure infections partial starvation occurs, so that the acetonuria has often received unwarranted attention, while the actual cause of the illness is not detected.

There are, however, acute toxic conditions not uncommon in young children which are accompanied by sufficient amounts of acetone bodies to cause definite acidosis. It seems probable that the increased acetone body production is not the cause of this condition, but is merely an expression of the toxemia. The production of these substances, however, may be of great clinical importance. It is this type of case which I propose to discuss. The following history is cited in illustration.

M. C., four years of age. On February 6, 1917, patient seemed slightly ill, refused part of her breakfast, and had a temperature of 102° F. She had slept well the night before and awoke in good spirits. At this time the physical examination showed little of significance. The patient was well nourished, had a good color, but seemed slightly listless. The tonsils and pharynx were moderately congested, but no exudate was present. The temperature remained elevated (as shown by the temperature chart) and the child was at times somnolent and at others very irritable. She took moderate amounts of water and a small amount of food. She complained of no definite symptoms except slight pain on swallowing. During the second, third, and

fourth days of the illness she vomited several times, but this was in no way suggestive of cyclic vomiting. The blood count on the first day showed 21,000 W B C, with 76.3 per cent polynuclears, 21.8 per cent mononuclears, and 1.1 per cent. of eosinophils. The urine showed an excretion of 3.65 grams of acetone bodies determined as acetone during the first twenty four hours, 2.86 grams during the second, and 3.1 grams during the fourth day of the illness. On the first day the blood acetone was 78 milligrams per 100 c.c. of blood and the carbon dioxide of the blood plasma bound as bicarbonate (Van Slyke) was 43 volumes per cent. On the third day the blood acetone bodies reached 110 milligrams per 100 c.c. of blood and the plasma bicarbonate was 37 volumes per cent., a considerable degree of acidosis. At this time there was mild, though distinct, air hunger.

Normal infants excrete from 0.001 to 0.007 gram of total acetone bodies per kilo of body weight in twenty four hours (Vedder and Johnson). Vedder and Johnson found that in the first twenty four hours of starvation the average excretion of acetone bodies becomes 0.004 gram per kilo of body weight in twenty four hours. In longer starvation the excretion may reach 0.03 gram per kilo per twenty four hours.

Our patient weighed 17 kilos, so that on the first day her acetone body excretion was 0.21 gram per kilo, an amount far in excess of that occurring in starvation. The acetone bodies in the blood were also much above those ever found in simple starvation. Moore found 39.5 milligrams of acetone bodies per 100 c.c. of blood in an infant who had been starved for two days. In acute febrile diseases he found a blood acetone from 11.4 to 23 milligrams per 100 c.c. of blood. I have made a number of determinations of the total acetone bodies in infants and children with pneumonia and other febrile diseases accompanied by partial starvation, and have never found more than 46 milligrams of total acetone bodies per 100 c.c. of blood. The usual figures were much less. It is, therefore, quite evident that the high blood and urine acetone body content in this patient was not due to the effects of fever or starvation or a combination of the two.

On the first day of her illness this patient was given 1 ounce of

3 per cent solution of sodium bicarbonate by mouth every three hours, but despite this the acidosis increased, as shown by the figures cited. On the third day 10 grams of sodium bicarbonate was given subcutaneously in 3 per cent. solution, and on the following day the plasma bicarbonate had risen to 54 volumes per cent of  $\text{CO}_2$ . This amount is practically normal. From this time the child began to improve and there was no recurrence of the acidosis. On the fifth day qualitative tests showed no acetone or diacetic acid in the urine<sup>1</sup> (Fig 41)

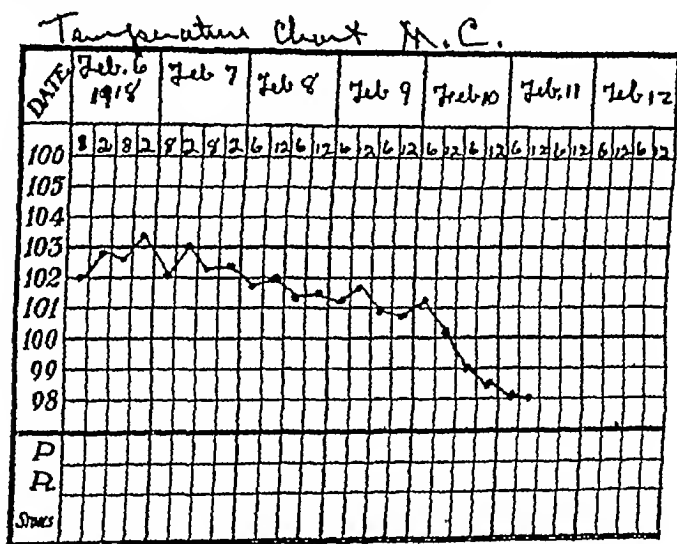


Fig 41—Temperature chart of M C

I have cited this case in some detail as an illustration of a type of toxic disturbance which is not infrequent. During the past two years I have observed 7 cases which come in this category. There are certain features of these cases which are of sufficient interest to discuss.

There is a tendency for such conditions to occur in families. In three families there were two children affected, and in each instance the second child became ill eight to ten days after the

<sup>1</sup> Howland and Marriott cite cases of obscure acetone body acidosis which are apparently of this type.

first The nature of the illness was similar in all The pharyngeal congestion was constant and in all there was leukocytosis This circumstance suggests two possibilities (1) that the condition is due to an infection, or (2) that there is a family predisposition to this type of metabolic disturbance At the present time our available data and methods of investigation are too limited to determine which condition is true Howland and Marriott have shown that in ileocolitis there may be a very marked increase in the acetone bodies in the blood It seems quite possible that this may be due to the direct action of the infectious agent If this assumption is correct it seems possible that other infectious agents may have a similar effect

There is also an individual predisposition to this type of disturbance Several of the children have had more than one attack, and the history of a boy of four years of age is of sufficient interest to cite He had an attack, similar to that of our first patient, in January, 1918 In March, 1918, he became acutely ill, and during the first two days his urine contained large amounts of acetone bodies On the second day the carbon dioxide tension of the alveolar air was 30 millimeters, indicating a distinct acidosis He had a slight coryza, pharyngeal congestion, and rhinitis He vomited a number of times On the third day Koplik's spots were present on the buccal mucous membrane and on the fourth day the rash of measles appeared This boy, therefore, developed a distinct acetone body acidosis with measles

There seems reason to believe that the underlying toxic condition in these attacks of obscure acetone body acidosis and that responsible for cyclic vomiting are of similar nature In many of the cases of acetone body acidosis vomiting occurs, although it is not as severe or as prolonged as in cyclic vomiting In some instances, however, a patient will have an attack of cyclic vomiting at one time, and at another an attack of acetone body acidosis without severe vomiting This circumstance was observed in two patients

A boy of six years had two attacks of cyclic vomiting and one attack of acetone body acidosis, without severe vomiting,

during the course of nine months. Another patient, a girl five years of age, had one attack of typical cyclic vomiting and one attack of obscure acetone body acidosis within a period of seven months.

The severity of the illness in these cases of acetone body acidosis varies greatly. The case cited at the beginning (M. C.) represents a type of moderate severity. The disturbance may be so severe as to cause death within twenty-four hours. The following case is an example of the fulminating type.

W. G., four years of age, had never been acutely ill, but had been subject to mild digestive disturbances. On February 4, 1918, he seemed slightly listless, but ate with good appetite. On February 5th, at 2 A. M., he awoke his nurse, complained of nausea, but did not vomit. At 9 A. M. he was acutely ill. At this time he was semistuporous, but could be roused. Temperature was  $104^{\circ}$  F., respirations were distinctly of air-hunger type. His extremities were cold. There was considerable swelling and congestion of the tonsils and pharynx. The carbon dioxide tension of the alveolar air was 22 millimeters and qualitative examination of the urine showed large amounts of acetone and diacetic acid. Blood withdrawn at 9 A. M. showed 140 milligrams of total acetone bodies per 100 c.c. of blood, and the plasma bicarbonate was 36 volumes per cent. of carbon dioxide. Despite the administration of sodium bicarbonate the child died at 5 P. M., after an illness of about fifteen hours.

As a contrast to this case there are others which are exceedingly mild. These mild cases apparently represent the same type of disturbance. The following is an example.

A well, sturdy boy, nine years of age, complained of abdominal pain at 5 P. M. and vomited once. His temperature at 6 P. M. was  $104^{\circ}$  F., and he complained of being uncomfortable, but was not acutely ill. He seemed rather listless. The pharynx was considerably congested. Urine voided at this time contained 0.3 gram of total acetone bodies per 100 c.c. At 10 P. M. the carbon dioxide tension of the alveolar air was 31 millimeters and the temperature  $101^{\circ}$  F. Blood withdrawn at this time showed 86 milligrams of acetone bodies per 100 c.c.

On the following morning the temperature was normal, and beyond a slight sore throat the boy seemed well. There were no further disturbances, and on the next day, thirty-six hours after the onset of the attack, he attended school.

In six of the patients there has been an evident inflammation of the tonsils and pharynx during the attack. Just what relation this bears to the actual cause of the toxic symptoms is difficult to determine. It seems quite possible, however, that this inflammation may represent an infection which is the causative factor just as the infectious agent of ileocolitis may be responsible for the acetone body acidosis which occurs in this disease. It is of sufficient interest to note that two children who were subject to cyclic vomiting and also to attacks of obscure acetone body acidosis, always developed pharyngitis and tonsillitis at the time of the attack. In the intervals between attacks the tonsils showed no enlargement, but were always much enlarged at the time of the attack. In both cases the tonsils were removed and were found to be filled with purulent deposits throughout their substance. Neither child has had a subsequent attack of either variety during the year which has elapsed since the tonsils were removed.

It is of interest in this connection that Sedgwick has observed in a number of children that the removal of adenoids has been followed by cessation of attacks of cyclic vomiting. It seems possible that in these cases the adenoid tissue harbored some infectious agent.

The treatment of these cases of obscure acetone body acidosis is obviously unsatisfactory, since we know so little of their true nature or of the causative agencies. Abundant water should be given, and if not taken by mouth should be given subcutaneously or by intraperitoneal injection. The presence and degree of acidosis should be accurately determined by means of the carbon dioxide tension of the alveolar air or, preferably, by estimation of the plasma bicarbonate. On the basis of these tests sufficient sodium bicarbonate should be given to correct the acidosis. It may be given by mouth, subcutaneously, or intravenously, according to the degree to which the alkali

reserve is impoverished The tonsillitis and pharyngitis should be treated by the usual measures

The features of importance of the type of disturbance which I have described may be summarized as follows There is a type of severe toxic disturbance in infants and children which is accompanied by a marked increase in the acetone bodies in the blood and a marked increase in the elimination of acetone bodies in the urine This may be due to an increased production of these substances produced in a normal metabolism, or to a combination of both Mild or moderate destruction of the amounts of increase in the acetone bodies is not due to starvation, but is probably due to the effect of some toxic agent on metabolism Fever is always present, and mild or moderate tonsillitis and pharyngitis are frequent There is a tendency for the attack to recur and for children in the same family to be affected It seems probable that there is some relationship between these obscure toxic conditions and cyclic vomiting

## CLINIC OF DR. JOSEPHINE B NEAL

WILLARD PARKER HOSPITAL

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### EPIDEMIC MENINGITIS<sup>1</sup>

Salient Features in the Diagnosis and Treatment of Different Types of Epidemic Meningitis Differential Diagnosis Important Sequelæ Serum Therapy Late Administration. Necessity of Prolonged Administration. Epidemic Meningitis in Infants. Types of Serum Reaction. Importance of Fehling's Reduction. Diagnosis Where Organisms Cannot be Demonstrated. Intravenous Injection. Autogenous Vaccine.

MENINGITIS is a disease not often seen except in time of epidemic. Consequently, when the general practitioner encounters a case he is often at a loss, first, in establishing the diagnosis, and, second, in conducting treatment. Almost everyone in the profession is aware that the chief therapeutic weapon is antimeningitis serum, but many are not aware that there is considerable difficulty to be encountered in administering this serum, much more so, in fact, than with diphtheria antitoxin. This being so, it is advisable to have the serum administered by someone trained in this special work and one who is also particularly experienced in confirming the diagnosis already tentatively established by the clinical signs. Consequently, the chief problem that confronts the attending physician is one of diagnosis, and the following cases have been selected with a view to rendering this problem a little less difficult by setting forth the salient features exhibited by these patients suffering from epidemic meningitis. These few cases have been selected from over 400 studied in the past eight years in connection with the work on

<sup>1</sup> Clinical lecture delivered to a special class of selected physicians May, 1918.



meningitis for the Research Laboratory of the Department of Health, because they bring out points of especial interest and value in arriving at the true nature of the picture that confronts one brought, perhaps for the first time, face to face with a serious condition that can, nevertheless, in most instances be successfully handled

The first case is presented to show the possibility of brain abscess occurring as a complication in meningitis, and to point out the value of the reduction of Fehling in the examination of the spinal fluids

CASE I —S K, six years of age The illness began on March 10, 1915, with pain in the ear and nausea On the following day the patient was admitted to a hospital, with severe headache, pain in the neck and eyes, photophobia, loss of appetite, and constipation Temperature  $102.3^{\circ}$  F, pulse 130, respiration 44 There was stiffness and retraction of the neck, a Kernig, and hyperesthesia, 30 c c of cloudy fluid were withdrawn at once On the 12th of March, when I first saw the patient, her condition was very much the same, but, in addition, a macular eruption was noted and also the presence of MacEwen's sign The knee-jerks were normal Examination of the eyes was resisted, but a day or two later it was observed that a hypopyon of the left eye was present Temperature  $100^{\circ}$  F, pulse 144, respiration 36, 25 c c of cloudy fluid were removed and 20 c c of antimeningitis serum injected This fluid showed a great increase in cells, 95 per cent polymorphonuclears, a few Gram-negative diplococci, mostly intracellular, a + + + albumin and globulin, and an absence of glucose A pure culture of meningococci grew at the end of seventy-two hours

On March 13th the condition was not so good Temperature was  $102^{\circ}$  F and the pulse was very weak, 20 c c of fluid were withdrawn and 15 c c of serum injected This fluid gave findings similar to the preceding, except that it was sterile

On March 14th the general condition was somewhat better, 35 c c. of fluid were withdrawn and 20 c.c. of serum given This fluid, like the preceding, was sterile, though a few organisms were seen in the smear

On March 15th the patient was somewhat weaker, the pulse being imperceptible at times, 25 c.c. of fluid were withdrawn and 20 c.c. of serum injected. This showed again a pure culture of meningococci.

On March 16th the condition and pulse were better, though the pulse was still rapid, 40 c.c. of cloudy fluid were withdrawn and 20 c.c. of serum given. This fluid showed a few organisms in the smear, but no growth.

On March 17th the condition was better, 40 c.c. of much clearer fluid were withdrawn and 20 c.c. of serum given, also 500,000,000 of an autogenous vaccine were given, as the organisms had been persisting in the fluid. This fluid showed one colony of meningococci and, for the first time, a slight reduction of Fehling appeared.

On March 18th 40 c.c. of nearly clear fluid were withdrawn and 20 c.c. of serum injected. This fluid was negative by smear and culture, the percentage of polymorphonuclears had dropped to 80 per cent., and there was a good reduction of Fehling.

On March 19th, 20th, and 21st the patient's condition was so much improved that no puncture was indicated. She became rational, at intervals previously she had been delirious. Her temperature ranged from 99° to 101° F and her pulse became slower, from 84 to 126, and of better quality.

On March 22d, as the temperature remained above normal and she was suffering from headache, a lumbar puncture was done and 40 c.c. of nearly clear fluid removed and 10 c.c. of serum injected. In addition, 750,000,000 of vaccine were then given. This fluid was sterile and showed considerable progress toward normal, the cells being only slightly increased, the albumin and globulin much less than in the preceding fluid, and a prompt reduction of Fehling.

On March 23d an urticarial rash appeared, and on the 24th 1,000,000 of vaccine were given. The temperature ran higher (up to 103.6° F) on this day, beginning at 8 A. M. before the vaccine had been given. On the 25th the temperature was still elevated, around 103° F, and the patient was drowsy, 50 c.c. of clear fluid were withdrawn, but no serum given. The fluid had

been nearly normal The failure to improve, therefore, was not due to the persistence of the meningitis

March 26th patient drowsy, temperature  $101^{\circ}$  to  $102.6^{\circ}$  F  
March 27th difficulty in swallowing, decided twitching on right side of face, temperature  $100.4^{\circ}$  to  $104^{\circ}$  F March 28th legs drawn up and movement resisted, unable to swallow, continual movement of left arm, temperature  $101^{\circ}$  to  $103.2^{\circ}$  F

March 27th condition about the same, 50 c c of clear fluid, practically normal, only a slight increase in albumin and globulin

March 30th and 31st and April 1st condition continued about the same On April 2d the condition was worse and 30 c c of slightly blood-tinged fluid were withdrawn

April 3d, 4th, 5th, and 6th the pulse and general condition were better, except that on April 4th she was unable to swallow for a time Temperature on these days ran from  $98.8^{\circ}$  to  $102.6^{\circ}$  F, the average being around  $100^{\circ}$  F On April 7th the condition became worse, pulse was very weak, and the temperature ran higher, to  $103.6^{\circ}$  F

On April 8th, 9th, 10th, and 11th the condition improved somewhat On the 12th 40 c c of clear, normal fluid were withdrawn Then the temperature began rising, reaching  $106.4^{\circ}$  F, pulse 144, respiration 40 On the following days the temperature continued to run high, reaching  $106^{\circ}$  F on April 13th and 14th,  $107^{\circ}$  F on the 15th,  $108^{\circ}$  F on the 16th, and  $108^{\circ}$  F on the 19th On the last day she died, showing marked emaciation and contractures An autopsy was performed and showed behind the fissure of Rolando in the right side a large abscess with evidence of extensive hemorrhage around it and in it Smears from this abscess showed no organisms The meninges were practically normal

In one other case that I saw only once in consultation a brain abscess was discovered at autopsy The history of this case has been duplicated in the essential details by at least three others, in my experience, where autopsies could not be obtained In these cases the spinal fluid became sterile In one instance it became clear and nearly normal in character, in one case it remained cloudy and failed to reduce Fehling, and in one case

it became yellowish, with a very high albumin and globulin content, suggesting a hemorrhagic condition and reducing Fehling to some extent. These cases all showed more marked signs of improvement than did the case presented here, and a favorable outcome was anticipated. Lumbar punctures performed after they became worse continued to yield sterile fluids. In all these cases marked and rapid emaciation occurred toward the end. In two instances there were unusually severe convulsions. Strumpell in 1889 was the first, I believe, to point out that brain abscess may arise in the course of meningitis, and he cited the history of 3 cases, apparently idiopathic, that had been preceded by meningitis. Fortunately, it seems to be a rather infrequent occurrence.

The presence or absence of glucose, as shown by the presence or absence of Fehling, has been commented upon in discussing this case. It has been our experience that the progress toward recovery usually runs parallel with the return of the power to reduce Fehling. Of course, glucose is present in normal spinal fluid. It becomes greatly diminished or lost at the height of the disease in all but the mildest cases of meningitis. As improvement occurs it gradually returns, though it frequently does not reach normal before the lumbar punctures are stopped. In certain cases that run a prolonged course the reduction of Fehling does not return even with a favorable outcome. In these instances the fluid is usually yellowish in color and shows a very high albumin and globulin content. Of course, not all cases recover in which the reduction returns. It naturally does not apply, for instance, to cases like the one described where the patient dies of a complication, not of the meningitis. But with the exceptions to which practically all rules, especially those relating to medicine, are subject, this holds very well. Not much has been written about it, and yet it is a very simple test to perform, and will serve as an index to treatment where it is not possible to have the spinal fluid cultured. Equal parts of Fehling and spinal fluid should be used and the degree of reduction should not be read for about an hour. A normal reduction taking place quickly is marked + + + (three plus)

The next case is presented to show the difficulties often encountered in diagnosing cases of epidemic meningitis, especially those of long standing. It also illustrates the fact that, even though instituted late, the serum treatment is of great value. Occasion is taken to discuss some of the most important sequelæ of epidemic meningitis.

CASE II.—M M, twenty-one months old. Seen first June 5, 1916. There was a history of illness extending over two months, beginning with an abscess from broken-down glands on the left side of the neck. After this there was a discharge from the right ear. Then there were symptoms of some pulmonary condition, evidently not a frank pneumonia. Later there was iritis and hypopyon of the right eye, together with rather indefinite meningeal symptoms. The child was sent to a hospital for diseases of the eye and some general improvement followed. A lumbar puncture was not done. The eye condition was not greatly improved. She had been home from the hospital only a short time when she again became worse and vomited very persistently, so that no nourishment had been retained and she had refused food for twenty-four to thirty-six hours. When I saw her she was stuporous. There was slight stiffness of the neck and a marked MacEwen. The knee-jerks were not obtained. The left pupil was dilated and did not react to light. The right was contracted and the tension of the eyeball markedly diminished. Pulse 140, regular, and temperature 99° F, it had been running a rather low, irregular course. The child was greatly emaciated.

The diagnosis of this case presented several difficulties. Clinically, it looked like a tuberculous meningitis: the low irregular temperature, stuporous condition, the late vomiting (which is usually early in epidemic meningitis), the emaciation, and the slight but well-marked stiffness of the neck. Generally a case of epidemic meningitis that has been running on for some time shows retraction of the neck. Furthermore, there was the history of broken-down cervical glands and an indefinite infection of the lungs, all strongly suggesting a tuberculous condition. On the other hand, there was the history of

hypopyon, which I had never seen in tuberculous meningitis, but which occurs occasionally in the epidemic form, and the pulse, though rapid, was regular. In tuberculous meningitis the pulse is usually irregular in rate and force. Then, again, the history of a running ear would suggest the possibility of a meningitis of otitic origin, probably caused by a pneumococcus or a streptococcus. A lumbar puncture yielded 35 c.c. of slightly cloudy fluid, and 20 c.c. of antimeningitis serum was immediately injected. This fluid showed a great increase in cells, 95 per cent. polymorphonuclears, a few Gram negative cocci both intra and extracellular, a pure culture of meningococci, albumin and globulin + + + +, and Fehling 0 + (a normal reduction of Fehling is marked + + +).

June 6th Temperature 100° F, pulse 140. Child had not vomited in the past twenty four hours and had taken some nourishment, 35 c.c. fluid withdrawn and 20 c.c. injected. The results of the examination of this fluid were similar to the first.

June 7th Condition about the same, 40 c.c. fluid somewhat clearer, and 20 c.c. serum. This fluid was similar to the other except that the reduction of Fehling was still more diminished. The organisms failed to grow, though they were still present in the smear.

June 8th, 9th, 10th, and 11th Lumbar puncture was done each day, amount of fluid removed varying from 30 to 40 c.c., and 20 c.c. of serum were injected each time. The fluids were all free from meningococci both by smear and culture. The number of cells gradually decreased and so did the percentage of polymorphonuclears. The reduction of Fehling continued to be greatly diminished until the 10th, when it became + +, and on the 11th it was + + +, or normal. The general condition improved slowly, nourishment was very well taken and there was no vomiting. The dilatation of the left pupil, which had been very marked at first, gradually became less.

June 30th As the child had been restless and had not slept well for two or three nights, a puncture was done to relieve pressure, 35 c.c. clear fluid were removed and no serum was given. This fluid still showed considerable increase in the albu-

min and globulin, though the number of cells was only slightly increased, 95 mononuclears, and the reduction of Fehling was practically normal. Although the meningitis had cleared up and the child took nourishment well, the nutrition did not improve and she remained greatly emaciated.

Early in July, on account of the continued emaciation, the patient was sent to a hospital for babies to see if the nutrition could not be improved by suitable feeding. Although she did improve somewhat during her stay in the hospital, when seen at home in August she was still greatly undernourished and had an excessive growth of hair on the extensor surfaces of the arms and legs and on the back. Soon after this, however, she began to improve, gained in weight and strength, and began to walk and talk again. As the nutrition improved the excessive growth of hair disappeared.

When seen in January, 1917, she was a very healthy, well-developed child, intelligent and playful, and seemed quite normal in every way except for the loss of sight in her right eye. The right eyeball was atrophied.

This excessive growth of hair, associated with the profound malnutrition, I have seen in one other case that came under my observation late and gave a history strongly suggesting an attack of meningitis. Netter and Debre are the only workers in whose writings I have seen this condition mentioned. They make no suggestion as to the cause of the condition. It may very well be due to some disturbance of the internal secretion resulting from the long-continued meningitis.

Loss of eyesight, due to an iridochoroiditis of which the hypopyon is a symptom, and deafness are possibly the two most serious sequelæ of meningitis. The loss of eyesight is usually limited to one eye. In one instance only have I seen it occur in both eyes. In 410 cases it has occurred ten times. There is a difference of opinion as to the manner in which the infection reaches the eye, according to some it is borne by the blood, while others think it proceeds by extension along the pia arachnoid of the nerves. Councilman, Mallory, and Wright hold the latter opinion and back it up by autopsy findings. The loss

of eyesight is usually complete and the eye becomes smaller. In one instance only did the inflammation subside without resulting in so much destruction, and at the end of a year there was some vision present.

Deafness is a more common sequelæ. It usually affects both ears and is complete and permanent. Ordinarily it comes on during the height of the illness, and in young children may not be observed until convalescence. In one instance it appeared two or three weeks after the treatment had stopped, and in one case there was a partial deafness in the acute stage, which cleared up almost wholly during convalescence, but reappeared suddenly and became absolute about nine months later, when the child was hit on the back of the neck by a falling slab. The blow was not very severe, not sufficiently so, apparently, to cause serious injury, and the deafness does not seem to have been due primarily to it. Perhaps it was instrumental in starting up some latent inflammatory process. The auditory nerve, according to Councilman, Mallory, and Wright, in cases of deafness shows exudative and degenerative changes due to the extension of the inflammatory process from the meninges. This process may extend and involve the labyrinth and even the organ of Corti. The fibrinopurulent exudate is soon organized into an osteoid connective tissue. Those rare cases of deafness that clear up are probably due to a serous infiltration of the labyrinth and nerve which readily subsides. In 410 cases deafness has occurred in 20.

The next case is presented to show the possibility of diagnosis and treatment in a very young child. It must be borne in mind that before the introduction of serum therapy the mortality in children under a year old was nearly 100 per cent.

CASE III.—J. P., fourteen weeks old, first seen April 4, 1918. Illness began March 27th suddenly, with fever and restlessness. There had been no vomiting, but the stools had been greenish. When seen there was a bulging fontanel, the child lay with head retracted, and was very restless. There was a temperature of 101.2° F. Most cases of meningitis in children under a year old do not show stiffness of the neck or retraction, but usually



if the child is held on the side there is a tendency for the head to fall back. The Kernig is usually of no value, as the child is irritable and resists the gentlest handling, and the reflexes are difficult to elicit. The fontanel usually bulges, but an absence of tension does not absolutely rule out an increased pressure of fluid. Netter says "In times of epidemic think of meningitis and do a lumbar puncture on every child sick without apparent cause." A lumbar puncture was done and 20 c.c. of cloudy fluid removed showed a great increase in cells, 95 per cent polymorphonuclears, a ++++ albumin and globulin, an absence of the reduction of Fehling, Gram-negative diplococci both intra- and extracellular, and a pure culture of meningococci, 20 c.c. of serum were injected at the time the puncture was done.

On April 5th and 6th 25 and 20 c.c. of fluid were withdrawn respectively and 20 c.c. of serum injected each time. Both these fluids showed no meningococci by smear or culture.

April 7th. As the case seemed much improved and the fluid was sterile by a forty-eight-hour culture, no puncture was done. The case continued to do very well and made an uneventful recovery.

Certain writers have a table of dosage of serum for children neatly arranged according to age. It has been my experience that in young infants as well as in older people the amount of serum should be regulated by the amount of fluid withdrawn and the ease with which it runs in by gravity, and I never hesitate to give 20 c.c. even to young infants. This is in accordance with the practice of most of those who have had much experience with young children. Indeed, some recommend doses of 30 c.c. or even more.

The next case is presented to show the necessity of persisting with the serum treatment even when the case yields very slowly to it.

CASE IV—J. G., twenty-four years old. Illness began September 8, 1917, suddenly, with headache, restlessness, chills, and fever. Seen September 9th. Moderate stiffness of the neck and Kernig. Pupils slightly contracted, equal, and react-

ing to light. Knee-jerks equal and slightly increased Irritable. Pulse 84, regular Temperature  $104^{\circ}$  F, 35 c.c. very cloudy fluid, 20 c.c. serum This fluid showed a great increase in cells, 95 per cent polymorphonuclears, + + + + albumin and globulin, and an absence of the reduction of Fehling There were extracellular Gram diplococci in the smear, but the culture was sterile.

September 10th 50 c.c. of cloudy fluid, 20 c.c. of serum This fluid was similar to the first, except that it yielded a pure culture of meningococci.

September 11th, 12th, 13th, 14th, and 15th Lumbar punctures done daily, 20 to 50 c.c. of fluid being removed, and 20 to 35 c.c. of serum injected The fluid gradually became clearer and the reduction of Fehling returned, but the cultures remained positive until the fluid of the 15th, which was sterile It was also nearly clear and gave a practically normal reduction of Fehling The patient's general condition was good and the temperature was normal

September 19th Another puncture was done, as there had been fever and headache during the night, 45 c.c. of slightly cloudy fluid were withdrawn and 35 c.c. of serum injected. Although three or four colonies grew at the end of forty-eight hours, no more punctures were done until the 24th. Some physicians believe that after a fairly large amount of serum has been given the patient can take care of a few organisms if left to his own devices While this is not in accordance with our views, it seemed best to try out this theory in this particular instance The patient's condition continued to be good and the temperature remained normal until the 24th, when he became worse and had a temperature of  $103^{\circ}$  F

September 24th, 26th, 27th, and 28th Punctures were done daily, 40 to 45 c.c. of fluid being removed and 20 to 35 c.c. of serum being given. These fluids all yielded cultures of meningococci except the one on the 28th, and the reduction of Fehling had gradually disappeared, 500,000,000 autogenous vaccine were given.

September 29th, 30th, October 1st, 3d, 4th, 5th, 6th, 7th

Lumbar punctures were done daily and serum given. These fluids showed positive cultures up to the 6th and 7th, when they were sterile and showed a fairly good reduction of Fehling. Meantime the vaccine had been given every two or three days and increased to 4,000,000,000. The patient's condition seemed remarkably good for so long an illness. He seldom had fever except for a little while during the reaction from the serum. He was occasionally delirious at night.

October 9th. Another puncture was done and 30 c c. of nearly clear fluid removed and 20 c c serum given. One colony finally grew from this fluid, 6,000,000,000 vaccine were given. No other puncture was done until the 13th and the condition was very good. On the night of the 12th, however, he had temperature, 35 c c slightly turbid fluid were withdrawn and 30 c c administered, 8,000,000,000 of vaccine were given. This vaccine apparently caused some reaction, as there was more fever, headache, and restlessness than ordinarily followed the administration of serum alone. This fluid showed some growth, but the fluids of the 14th, 16th, 17th, and 18th were sterile. On the 15th 10,000,000,000 vaccine were given, which was also apparently followed by some reaction. These last four fluids were rather less in amount than the earlier ones, running from 5 to 15 c c. They showed a fair reduction of Fehling, the last two practically normal. Although the patient was considerably emaciated, he made a rapid and complete recovery.

This case illustrates very well the necessity of continuing the serum treatment even if a good many injections are necessary. In all, twenty-eight doses of serum were given, and it would seem that the recovery was due to the persistence in administering it and perhaps to the additional action of the vaccine, for on the two or three occasions when the serum was stopped, because the patient's condition and the sterility of the fluid or the very small number of organisms seemed to warrant it, he promptly got worse. That is, he was given the opportunity two or three times to go on to recovery by himself without the serum and he was not equal to it. In several instances in my experience it has been necessary to give from twelve to twenty injections in cases that

have finally recovered, but this is, up to the present, the largest number. One of the causes of lack of success in the serum treatment is the failure to persist in cases like this.

Where the organisms persist after five or six injections, or where lapses occur, it is well to use an autogenous vaccine. It is often difficult, as in the present case, to tell whether or not it does any good, especially if the serum is continued with it. It is to be observed, however, that after the reaction following the 8,000,000,000 administered on the 13th the fluid was sterile. In an adult it is quite safe to begin with a dose of 1,000,000,000 and to continue with 2,000,000,000, 4,000,000,000, 6,000,000,000, 8,000,000,000, and even 10,000,000,000 if a reaction does not occur earlier.

The next case is an illustration of those in which symptoms of sepsis predominate rather than those of meningitis, and where reaction to the serum is so severe that its use cannot be continued. The various forms of serum reaction are discussed.

CASE V—M. D., three years of age, onset October 30th, with vomiting, irritability, and fever. A purpuric rash appeared on the body and the joints of the left wrist and thumb became swollen and tender. On November 3d a blood-culture yielded meningococci. A septic temperature was running, ranging from 98° to 105° F. Although there were only slight signs of meningitis, a lumbar puncture was done November 5th and 30 c.c. of bloody fluid were withdrawn, which the physician doing the puncture believed to be hemorrhagic, and about 30 c.c. of serum were given by gravity. The child immediately became cyanotic and pulseless. Artificial respiration, massage of the heart, stimulants, and oxygen were given and the condition improved. The spinal fluid showed no meningococci. The amount of blood interfered with the other tests. The child's evident intolerance of serum made it inadvisable to try the intravenous administration, although she continued to run a temperature, but not so septic as the first three or four days. The rash was fading by November 7th, although the joints continued to be swollen and painful. On the 9th the face began to be swollen and examination of the urine showed an acute nephritis. On the 14th a blotchy rash,

evidently a serum rash, appeared on the body and lasted for several days. The temperature from the 11th to the 14th ran a lesser course, around  $100^{\circ}\text{F}$ , but on the 15th it shot up again to

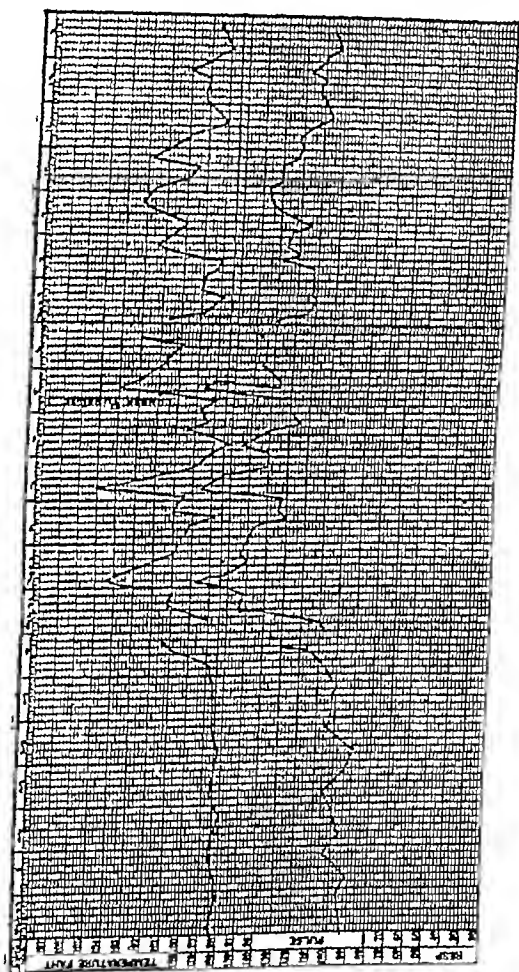


Fig 42 —Chart of Case V

$105^{\circ}\text{F}$  The child seemed very sick and vomited a good deal on the 16th and morning of the 17th, this might have been due to the nephritis or the serum reaction. The temperature began running lower on the 17th and continued to run a lesser course

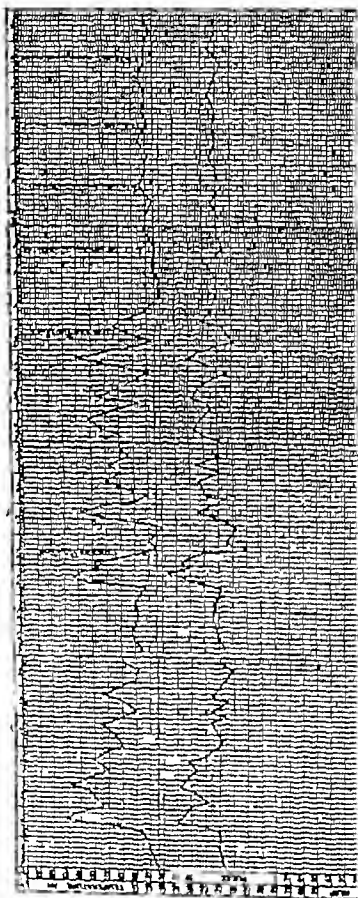


Fig 43—Chart of Case V (Continued)

until the 23d, when it went up to 104 2° F. A second lumbar puncture was done on the 24th, although there were no well-marked signs of a meningitis, 30 c c of nearly clear fluid were withdrawn, but no serum was given. This fluid showed a great increase in cells, 85 per cent polymorphonuclears, a ++ albumin and globulin, a +++ Fehling, and no meningococci by smear or culture. This might very well represent fluid of a recovered case of meningitis. The patient continued to run a septic temperature, and on December 1st a third lumbar puncture was done, 30 c c of distinctly cloudy fluid were withdrawn and 20 c c. of serum were again given, in the hope that there might be no reaction this time, and, at any rate, desperate measures seemed warranted. A severe reaction followed, however, and no more attempts were made to give serum, although this fluid showed meningococci both by smear and culture. On the following day, December 2d, however, the temperature dropped to normal. An autogenous vaccine was prepared and its use was begun on the 4th with 250,000. The vaccine was given every other day for five days, running it up to 1,500,000,000. The temperature continued to be practically normal and recovery took place. Urine examination on December 11th showed that the nephritis had cleared up.

This case is interesting from a number of points of view. In the first place, the symptoms of sepsis were much more prominent than those of meningitis. A good deal of attention is being paid to cases of this sort at present because they have occurred in a larger proportion than usual in some of the army camps. Indeed, Herrick goes so far as to say that the meningitis is a secondary complication of the early sepsis. This seems to me an extreme view. No doubt there is an early sepsis in many, perhaps in most, cases of meningitis, but so is there in pneumonia and typhoid. But it is the pneumonitis and intestinal ulcers that we have to consider, not the sepsis. So it is, I think, in the great majority of cases of meningitis, though, of course, in certain outbreaks there is a larger than ordinary number of cases where the sepsis predominates. In the cases appearing in New York City during the past eight years certainly the number of septic cases has been comparatively few. Of course, cases of this sort should be given

serum intravenously Herrick recommends 50 to 100 c.c., repeated in eight to twelve hours. The intraspinal injections should not be neglected if the spinal fluid shows that the meninges have been involved. This point of not neglecting the intraspinal injections cannot be too strongly emphasized, as many physicians have seemed to gather the impression that perhaps the intravenous method is preferable and, indeed, may supplant the intraspinal administration.



lyzed The serum reaction seems to be little influenced by the quantity of serum given, and from the time of its appearance is caused by the first dose Indeed, one of the severest reactions I have ever seen followed a single dose In cases that relapse and require the readministration of serum at an interval of several days after the first series of injections have been given, we have on several occasions observed an urticarial eruption appearing in twenty-four to forty-eight hours This same accelerated reaction also occurs with other sera The rash of either the usual or the accelerated reaction may come out every day for several days and be accompanied by fever (3) There may be a true anaphylactic reaction to the serum, which, fortunately, is very rare In only this one case has there been so much hypersensitiveness that it was impossible to use it

The next case is introduced to illustrate a not unusual type where, although the clinical symptoms and the response to serum point to an epidemic meningitis, the organisms cannot be demonstrated, the examination of the spinal fluid, apart from the bacteriologic side, however, confirming the diagnosis of an acute meningitis

CASE VI—M R, twenty-three years of age Sudden onset on the afternoon of August 16, 1917, with headache, fever, vomiting, and wild delirium First seen twenty-four hours later, vomiting, headache, and delirium continued Combined efforts of three people necessary to restrain her while puncture was done There was stiffness of the neck and a marked Kernig Pupils reacted to light The knee-jerks were absent Pulse, 72 regular Temperature 103° F, 35 c c of cloudy fluid were obtained and 20 c c of serum injected This fluid showed a great increase in cells, 95 per cent polymorphonuclears, ++++ albumin and globulin, and a + Fehling, but no organisms could be demonstrated either by smear or culture About twelve hours elapsed, however, between the withdrawal of the fluid and its examination

August 18th The condition had improved remarkably She was rational, the vomiting had stopped, and the temperature was 100.4° F, 45 c c of slightly cloudy fluid were obtained and

20 c.c. of serum injected This fluid showed about the same findings as the preceding one, except that the number of cells was diminished and the reduction of Fehling was ++ 1

August 19th The temperature was 99.6° F in the morning, but fell to normal during the day, 35 c.c. of nearly clear fluid were withdrawn and 20 c.c. of serum injected This showed fewer cells and a normal reduction of Fehling The albumin and globulin were still greatly increased As the fluids had been sterile and the clinical symptoms had entirely subsided, no more punctures were done She made an uneventful convalescence. An urticarial rash appeared on the 25th and lasted three days

Of course, the diagnosis in this case was not proved bacteriologically, but clinically it was a case of an acute meningitis The spinal fluid showed an active, purulent, inflammatory reaction in the greatly increased cells, with the 95 per cent. polymorphonucleosis, the high albumin and globulin content, and the diminished glucose as shown by the poor reduction of Fehling Moreover, the case responded promptly to the use of anti-meningitis serum. In view of these facts, and also of the fact that all other forms of purulent meningitis—pneumococcic, streptococcic, staphylococcic, and influenzal—are so uniformly fatal, there seems little doubt as to the true diagnosis We have had one case of streptococcic meningitis recover, but all other cases of purulent meningitis due to the organisms mentioned above have died

Confusion in diagnosis may arise in a case of so-called meningitis sympathetica, a condition occurring where there is inflammation near the meninges Several cases of this kind are described by I. Strauss He characterizes the fluids as showing an increase in pressure and in the albumin and globulin content and cellular elements, the cells being usually polymorphonuclears The fluids are also sterile He makes no comment as to the sugar content except in one case, where he says it was increased In two cases of this type that I have seen the reduction of Fehling has been normal A diminution in the reduction of Fehling may, therefore, be of help in ruling out this condition, as well

as the failure to find any evidence of a focus of infection in the vicinity of the meninges

In stating that I believe the diagnosis of epidemic meningitis to be probably correct in cases like M R where there are symptoms of an acute meningitis, a favorable response to anti-meningitis serum, a fluid showing an increase in the polymorphonuclears and in the albumin and globulin, and a diminished reduction of Fehling, even though meningococci cannot be demonstrated, I by no means wish to imply that I believe an epidemic meningitis exists without the presence of meningococci. It is easy to see, however, that it is possible, if the organisms are few in number, for them to elude our attempts at demonstration even in an early case like this. Of course, the quantity of material used on the slides and on the culture-media is relatively small, and the organisms may not be in that particular quantity. The cultures sometimes show only one, two, or three colonies even in positive cases, and it is easy to understand that another portion of that same material might have contained an insufficient number of organisms to produce a colony. (In subculturing meningococci it is necessary to carry over a larger amount of material than is the case with most organisms.) Moreover, the meningococcus undergoes spontaneous autolysis, and if the spinal fluid cannot be examined within a short time, a few hours, the chances of demonstrating the organism become less. In this particular case the fluid was not examined for over twelve hours after it was withdrawn, and this may very readily account for the smear being negative and the culture sterile. In cases that have been running on for some time when first seen the organisms may have disappeared due to the action of the patient's own antibodies.

The important point about this is that patients of this type should receive the benefit of antimeningitis serum. If, as sometimes happens, after two or three sterile fluids some other organism makes its appearance, no harm will have been done for two reasons: first, the antimeningitis serum, while of no benefit, will not have been injurious, and second, not being able to foresee the organism that was about to appear, we could

not have used its specific immune serum earlier. Moreover, the treatment of all other forms of meningitis is highly unsatisfactory.

This question has been taken up somewhat at length, but it can hardly be too much emphasized that on doing a lumbar puncture a cloudy fluid should be followed immediately by the injection of antimeningitis serum, and that the use of the serum should be continued, even though the meningococci cannot be demonstrated, until the patient is greatly improved or until some other organism has made its appearance. This rule, naturally, will not apply to the cases of meningitis sympathetica where the cloudy fluid is due to an inflammatory focus in the neighborhood of the meninges.



## CLINIC OF DR. BURRILL B CROHN

### MOUNT SINAI HOSPITAL

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#### CLINICAL CONDITIONS CHARACTERIZED BY OBSTRUCTIVE JAUNDICE<sup>1</sup>

Difficulties of Diagnosis. Aid Rendered by Duodenal Tube Diseases Showing Common Symptom of Obstructive Jaundice and Methods of Diagnosis with Analysis of Cases Calculi in Choledochus, Carcinoma in Terminal Bile and Pancreatic Ducts, Sarcoma Involving Head of Pancreas, Chronic Intralobular Pancreatitis Value to Accurate Diagnosis of Ascertaining Patency of Biliary and Pancreatic Systems and Functional Activity of Pancreas

WE will devote ourselves today to the consideration of a series of cases possessing in common the clinical feature of obstructive jaundice. This type of case is one in which the exact diagnosis has at all times been associated with many difficulties and pitfalls. In fact, in no field of abdominal conditions have more surprises and unexpected findings been encountered at operation or at autopsy. To differentiate a benign obstruction from a malignant one has always been a matter of difficulty. We apply our keenest clinical insight, we make use of all our best laboratory data, and yet even then we are often puzzled to determine the exact etiologic factor in our case of obstructive icterus.

Of recent years we have noted the introduction of the duodenal tube as an aid in the diagnosis of such conditions. In this clinic I shall attempt to demonstrate the mode of applying the chemical data obtained by means of the tube to the clinical

<sup>1</sup> Impromptu clinical demonstration delivered in the wards of Mount Sinai Hospital, service of Dr. Emanuel Libman May 1918.

facts in hand, and shall show to what extent this data can be applied in the interpretation of the clinical phenomena

The first patient is a man forty-eight years old. During childhood he suffered from a severe attack of pharyngeal diphtheria, he also had measles. He denies all venereal disease. He married twenty years ago, his wife has given birth to four healthy children and has had no miscarriages. He has never, to his knowledge, had typhoid. He is very mildly alcoholic, drinking an occasional glass of beer. Ten years ago he suffered from an attack of acute abdominal pain, localized, as he says, in "the pit of the stomach." The pain was cramp-like, lasted for two hours, and was relieved only by a hypodermic injection of morphin. From time to time since then he has experienced similar though less severe attacks of pain. Since the original attack he has suffered from "heartburn" one to two hours after eating. Meat in particular gave rise to this sensation. He experienced relief when taking small doses of bicarbonate of soda, and violent belching usually denoted the end of the attack. He vomited only once, the vomitus consisting of food recently eaten and containing no blood. He has never noted blood in the stools nor tarry feces.

During the fortnight previous to his appearance for treatment he was seized almost daily with several attacks of abdominal cramps lasting, on an average, fifteen minutes. Twelve days before I saw him he noticed that his skin was becoming yellow. The depth of this coloration gradually increased until it was a dark yellow shade. His stools became clay colored in appearance, though he was somewhat constipated. He also lost 8 pounds in weight.

Physical examination revealed a well-nourished, rather obese man, weighing 190 pounds and of average height. As you see him today after his operation he is not jaundiced, but previously his skin was a deep icteric hue, golden yellow in shade. On exposing his abdomen you will see a long transverse scar across the upper quadrants. On abdominal examination made before operation one could palpate a slightly enlarged liver edge extending two fingerbreadths below the free border of the ribs,

and an area of slight tenderness extending from the right of the right rectus muscle to halfway between the ensiform cartilage and the umbilicus. There was also tenderness over Murphy's point, though the gall bladder was not palpable. Temperature was normal, pulse 84. Blood examination showed a low white cell count (7500 per cubic millimeter), with a polymorphonuclear count of 80 per cent.

From what form of jaundice was this man suffering? What was the etiologic factor in his illness? To all intents and purposes the patient was suffering from an obstruction of the common bile-duct, probably from a calculus which had worked its way down through the cystic duct and was now lodged somewhere in the common duct. Was the common duct partially occluded, or was it completely obstructed, and, if the latter, was the pancreatic duct also involved?

At this point we turn to the evidence obtained by chemical examination. The duodenal tube was passed one night at 10 o'clock, and the next morning the contents of the duodenum were obtained. They had a faintly golden yellow coloration and were clear. Bile was evidently entering the duodenum, although in diminished amounts. Chemical examination of the fluid showed the three pancreatic ferments—amylase, lipase, and trypsin—to be present in normal quantities.

Microscopic and chemical examinations of the stool gave no evidence of abnormality. There were no excessive amounts of muscle-fibers or neutral fat.

To summarize. Here was a middle aged, portly man, who for ten years had irregular attacks of abdominal colic and symptoms of gastric hyperacidity. After a more severe attack he became jaundiced within two weeks, the jaundice increasing rapidly and deepening, and the patient losing weight. The duodenal contents showed a partial obstruction of the choledochus, no obstruction of the pancreatic duct, and a perfectly functioning pancreas. There was, then, apparently a partial obstruction of the common bile-duct above the head of the pancreas and above the diverticulum of Vater. This we know to be caused most often by a gall-stone lodged in the common duct.



The patient was operated upon, and three irregular prismatic gall-stones were found in the choledochus just above the point where the duct enters and passes through the head of the pancreas. The stones were firmly implanted in the duct. The pancreas was palpated throughout and felt apparently normal. The stones were successfully removed through an incision in the first portion of the common duct, a cholecystectomy was then performed and drainage established. Recovery was uneventful.

The obstruction caused by a calculus or by calculi in the common duct is very rarely a complete one. Only once have I seen a case where two large, firmly impacted calculi caused a complete obstruction and a disappearance of the bile from the duodenal contents. A new growth at this point, which has become superficial within the intestinal lumen and has begun to undergo degenerative ulceration, may simulate a partial obstruction of this kind, but in that case we have other guides, as will be demonstrated in one of the subsequent cases. As a rule, a new growth gives a picture of complete obstruction of one or both ducts, and a stone that of a partial obstruction of the common duct. Pancreatic disease, as an etiologic factor, seemed unlikely in the face of the chemical data.

As a contrast to this case, let us study for a few minutes the history of the following patient. This man, forty-eight years old, was admitted to the hospital for observation, complaining that for eight days he had been becoming progressively more jaundiced. He recalled no symptoms prior to this. He had not lost weight, had no pain nor gastric disturbance, but was obstinately constipated. He abstained from the use of alcohol and denied venereal disease.

Physical examination showed a fairly well-nourished man, decidedly jaundiced, with a pale saffron hue of icterus. There was no evidence of loss of weight. The liver was palpable one fingerbreadth below the free border of the ribs on the right side. The edge of the liver was sharp and smooth and slightly tender. The gall-bladder was not palpable.

During the first two weeks of his stay in the hospital the

patient's temperature was slightly elevated, reaching at evening a maximum of 101° F. The later course was afebrile.

Blood count leukocytes 6400, polymorphonuclear leukocytes 59 per cent, lymphocytes 31 per cent, eosinophils 9 to 12 per cent.

The patient remained under observation for three weeks. During this time the jaundice gradually disappeared, temperature became normal, and all symptoms cleared up. The duodenal contents obtained during this time showed abundant, ropy, mucoid bile and active pancreatic ferments. Evidently both ducts were patent.

The case was regarded as one of probable catarrhal jaundice, and the man was discharged from the hospital under that assumption. Only one point in the evidence favored the theory of new growth, on several occasions chemical blood had been found in the stools (guaiac test), but this was finally attributed to hemorrhoids which were present.

This patient left the hospital at his own request, feeling quite well. Seven weeks afterward he was readmitted, stating that he had been free of symptoms for the first four weeks, at the end of which time he noted a gradual reappearance of the icterus. His stools became clay colored, urine dark brown, and he began to experience epigastric pains.

On re-examination, the liver was found to be palpable three fingerbreadths below the free border of the ribs. The liver edge was slightly irregular and tender, the gall bladder was palpable as a smooth, globular, tender mass. Temperature was now of a septic type, reaching 103° to 104° F. at night and dropping to normal in the morning. A definite leukocytosis was now present and blood was chemically present in the stool. We again obtained duodenal contents for examination, this time they showed a complete absence of bile, pancreatic ferments were present, though in diminished strength. Operation was decided upon and performed, and a small round tumor was felt occupying the site of the papilla of Vater. The tumor was the size of a 25-cent piece, infiltrated, and very firm. The common bile-duct was enormously dilated to the thickness of a man's little finger.

The head of the pancreas was partially infiltrated with tumor tissue. The liver was enlarged and studded on its surface with numerous miliary and larger abscesses. Drainage of the gall-bladder was the only surgical procedure attempted.

In this case we were dealing throughout with a carcinoma arising in the papilla of Vater and invading the exit of the common bile-duct and the pancreatic ducts, as well as the head of the pancreas. We had opportunity of seeing the development of this case at two different stages. At the first stage we deduce from our findings that the neoplasm, though still at an early stage of its growth, had begun to ulcerate on its intestinal surface, freeing both the involved ducts. The patient was definitely jaundiced on his first admission to the hospital, yet the jaundice rapidly diminished and disappeared and the duodenal contents showed both ducts patent. The only sign of an ulcerating neoplasm was the blood in the stool. On the second admission to the hospital we saw the case in a more advanced stage. The neoplasm had extended and had involved in its tenacious hold both the common bile-duct and the pancreatic duct. This was evidenced by the complete absence of bile and the partial diminution in the strength of the pancreatic secretion. We now had two more links in our chain of evidence: a definite leukocytosis and temperature of the so-called septic type. We were dealing with an infectious cholangitis arising in the sloughing neoplasm and ascending the bile-ducts and invading the biliary radicle in the liver itself. That blood was still present in the feces was another point in favor of an ulcerating neoplasm.

Thus the chain of evidence was complete, and the findings at the operating table of the tumor, the enormous dilatation of the choledochus, the globular, tense gall-bladder, and the neoplastic invasion of the head of the pancreas confirmed the previous deductions.

This case demonstrates the two rôles in which a tumor of the terminal bile or pancreatic ducts, or of the papilla of Vater, appears. Most commonly, such a tumor causes complete occlusion of one or both of these ducts. The best evidence of

this is the complete absence from the duodenal contents of bile, or of bile and pancreatic ferments. Less commonly we see such tumors in the stage of necrosis, with sloughing of the neoplasm on the intestinal surface. If this occurs, a partial re-establishment of the flow of these secretions may be noted in the duodenal contents. Ulceration and sloughing in the tumor is further proved by the presence of fever, leukocytosis, and melena, these symptoms furnishing the evidence of a secondary ascending cholangitis.

As a further demonstration of the points just illustrated I should like to quote from an interesting case observed by Dr N E Brill, and published by him in full in the New York State Medical Journal in 1912. I had the privilege of studying the duodenal contents of this case. The patient was a young man, eighteen years old, who was admitted to the medical service of Dr Brill at Mount Sinai Hospital. He had suffered for three and a half years with sharp attacks of abdominal cramps, vomiting of greenish material, and constipation. Six months before his admission to the ward his appendix had been removed under the impression that chronic inflammation of that organ was causing the symptoms. Soon after the operation the symptoms returned and two months later he became jaundiced. He had chills and fever every day and lost rapidly in weight, color, and strength.

In the hospital the patient was weak, drowsy, apathetic, and pale. He was markedly jaundiced. No abdominal mass was palpable. His blood examination revealed a condition of severe secondary anemia. His hemoglobin was estimated at 22 per cent (Sahli, corrected), R. B. C. 1,500,000, W. B. C. 13,000, polymorphonuclear leukocytes 85 per cent. Feces contained blood chemically, but no excess of muscle-fibers or neutral fat.

The patient remained under observation for three months, gradually emaciating, running a continuously abnormal though irregular temperature course, and showing a progressive anemia, until he died. He was deeply jaundiced throughout the period of treatment.

During his stay in the hospital duodenal contents were obtained on three occasions. The first specimen of fluid so obtained showed a complete absence of bile and pancreatic ferments. A month later a second specimen demonstrated again an absence of biliary secretion, but traces of pancreatic ferments. Still another month later the duodenal secretion contained traces of bile and the pancreatic ferments were now abundantly present.

At the autopsy, which was performed by Dr E Libman, a friable rounded-celled sarcoma was seen invading the duodenal wall and involving the head of the pancreas. Both biliary and pancreatic duct systems showed enormous dilatation as a result of this terminal obstruction. Secondary necrosis and ulceration, however, had in part liberated these ducts, so that the obstruction at death was no longer complete.

This case is in many ways similar to the foregoing one. The former patient was seen for the first time when the ducts were open, on later examination the ducts were found closed. The latter patient was first seen at the stage of complete occlusion of the ducts. Later, the soft friable sarcoma ulcerated and a partial patency of the ducts was re-established. These two cases give a fair impression of the course and of the means of diagnosis of tumors involving the terminal bile and pancreatic ducts. Yet one correction to this impression must be made before a rule can be established. In by far the largest percentage of cases tumors in this area cause complete obstruction of one and frequently of both ducts. In my experience, when one duct alone is involved it has always been the common bile-duct. The complete occlusion may not be permanent, but is present in every case at some time in its course, and is most easily and only truly demonstrated by an examination of the duodenal contents.

Benign stenosis, in contradistinction to the above, gives, as a rule of thumb, only partial occlusion throughout its course. The exceptions to this rule are few. In passing it should be noted that stricture of the common bile-duct, which occasionally follows upon incision and drainage of the choledochus,

often gives the picture of complete bile occlusion. These cases are very easy to distinguish.

We may now proceed to review a type of disease which is also characterized by an obstructive jaundice, but which differs from the above two types. I shall read to you the clinical report and the account of the postmortem findings of the following case.

This is the history of a man thirty-seven years of age, his previous history was of little interest, he denied luetic infection, had no serious illnesses, his habits were good, he smoked a few cigarettes and abstained entirely from alcohol. He was married and had two healthy children. Seven weeks before his admission to the hospital he was suddenly seized with an attack of abdominal cramps, situated in the epigastric region and radiating to the umbilicus, the cramps lasted for about one hour. After that he noticed a gradually increasing jaundice, pale colored feces, and a tendency to diarrhea, having two or three motions daily. There was a marked loss of weight after the onset of his illness, but he did not know the exact amount. He was admitted to the medical service of Dr. N. E. Brill, in whose ward I had the privilege of seeing the patient.

Physical examination revealed a poorly nourished individual whose skin and sclerae were of decided icteric hue. The liver was enlarged, the free edge of the right lobe being palpable three fingerbreadths below the free border of the ribs, the upper border of the right lobe percussing to the fourth interspace in the midclavicular line. A globular, slightly tender mass in the right hypochondrium was evidently the distended gall bladder, otherwise the abdominal examination was without points of interest.

The patient was kept under observation for several weeks in an attempt to establish a diagnosis. Clinically, this was difficult, as many factors entered into consideration. The onset of the illness with an attack of abdominal pain suggested cholelithiasis with a calculus in the common bile-duct. On the other hand, the almost painless course, the progressive icterus, and the rapid loss of weight suggested a new growth. There were

no grounds for considering syphilis, the Wassermann reaction was negative. At no time during the period of observation was the temperature above normal, no leukocytosis was present, and there was no blood in the feces. A diagnosis of chronic pancreatitis was considered among the possibilities, though its rarity as a well-defined clinical condition causing obstructive jaundice spoke rather against it.

Duodenal contents were obtained and analyzed. A rather milky, slightly yellow secretion was withdrawn. Bile was present only faintly. On careful chemical analysis all three pancreatic ferments were found to be markedly diminished. It is interesting to correlate the duodenal secretion findings with the clinical data. A calculus impacted even firmly in the lower end of the common bile duct or in the diverticulum of Vater has never produced so marked an obstruction of the biliary outflow (always remembering the single instance where the rule was broken and the obstruction was a complete one). But apart from this, we have never seen a calculus produce so marked a diminution of pancreatic secretion. It is questionable whether a calculus lying in the diverticulum of Vater could sufficiently block both these excretory canals so as to cause the chemical picture seen here. Of course, a small calculus firmly impacted in the papilla of Vater could act as a complete plug, and so restrain the excretions of these two systems from entering the duodenum. But the practical fact remains that in our experience with a very large series of cases calculi do not give rise to so marked an obstruction as to cause both bile and pancreatic secretions almost to disappear from the intestine. It seems much more reasonable to suppose that the diminished pancreatic ferments were an indication of a pathologic process taking place in the pancreas, that is, a sclerosing pancreatitis, and that the common bile-duct in its final course through the head of the pancreas had become involved in the inflammatory process and its lumen markedly diminished.

We have, however, not yet excluded the possibility of a new growth at the head of the pancreas. We have seen from our previous two cases that a neoplasm, which involves the papilla

and is in the stage of necrosis, can give just such a picture in the duodenal secretion. But we lack the three clinical concomitants which are present in such a condition, namely, fever, leukocytosis, and melena. These three factors were entirely absent in this case.

In an attempt to substantiate the diagnosis of chronic pancreatitis the stools were carefully examined and found to be rather large and clay colored, and microscopic examination showed a large excess of undigested meat fibers and neutral fat globules. While the feces were not yet typical of advanced pancreatic disease, similar to the bulky, oily motions first described by Richard Bright, yet there was sufficient excess of undigested meat fibers and neutral fat globules definitely to denote a pathologic process in the pancreas.

Metabolism studies were performed to determine whether pancreatic disease had advanced to the point of interfering with intestinal absorption. The patient was put upon a mixed diet containing on an average 22 grams of nitrogen and 71.3 grams of fat per day. The feces were collected for three days, dried, and analyzed. It was shown that this man excreted 16.4 per cent. of his nitrogen intake and 34.7 per cent. of his fat intake. A person in normal health excretes from the alimentary canal only 4 to 6 per cent. of nitrogen and 12 to 16 per cent. of the fat of the diet. Evidently this patient had a definite disturbance of his ability to absorb food, that is, he had a steatorrhea and an azotorrhea. This, in the absence of intestinal disease, is pathognomonic of pancreatic disturbance.

At the operation performed upon this patient the upper abdomen was thoroughly explored. The gall bladder was found to be tense and distended. The wall was incised and the biliary ducts probed for their entire length. Neither calculus nor new growth was found. The head of the pancreas was indurated and exceedingly firm. Duodenotomy was performed to make sure that no neoplasm of the papilla of Vater had been overlooked, but none was found. Fine probes passed from above freely entered the enlarged choledochus, but met an impassable obstruction at the head of the pancreas. Attempts to



enter the ducts from the intestinal surface were also of no avail. A cholecystostomy was performed and the abdominal incision closed. The patient died in shock two days later.

At necropsy a chronic intralobular pancreatitis, mainly involving the head of the pancreas, was established as the cause of the symptoms. No other pathologic condition was discovered.

The foregoing case presents many points of unusual interest. It is an instance of a primary, chronic intra-acinar pancreatitis, a disease characterized by a proliferation of inflammatory connective tissue which invades and destroys the parenchyma of the gland and disorganizes the individual pancreatic lobules. It differs from chronic interlobular pancreatitis in that in the interlobular form the invading inflammatory tissue involves the periphery of the lobule, while the intralobular or intra-acinar form attacks the intimate secretory apparatus of the gland.

It is particularly the intralobular form of chronic pancreatitis in which one notes a diminution of the gland ferments in the duodenal fluid. Conversely, diminished ferments in the duodenal secretion denote a pathologic process in the pancreas. A new growth involving and obstructing the terminal pancreatic duct or the papilla of Vater acts differently. It usually obstructs the duct completely, then there is a complete absence of the ferments. Or, if ulceration has taken place in the tumor, the normal ferments pour through. The usual tumor is the small adenocarcinoma originating in and involving the papilla of Vater. This tumor does not destroy much of the pancreatic tissue. Hence, if the pancreatic ferments are at all present, they appear in undiminished strength.

Diminution in the strength of the ferments occurs in chronic intralobular pancreatitis, or in neoplasm involving and destroying the parenchyma of the gland. It is when the secretory acini are invaded and destroyed that the pancreatic secretion is disturbed. In acute pancreatitis the ferments are almost entirely absent. Duodenal contents in which bile is abundant but ferments diminished means always parenchymatous pancreatic disease, usually chronic inflammation.

Nitrogen and fat absorption is dependent not so much on the preservation of a copious and active external secretion of the pancreas as it is dependent upon the functional activity of the pancreatic parenchyma *per se*. Mere mechanical obstruction of the pancreatic duct system is not associated with disturbance of alimentary resorption. This has been repeatedly demonstrated in metabolism studies of cases of neoplastic obstruction of the ducts. Following the suggestion of Lombroso, who conducted careful experiments upon dogs, we have come to understand that it is the state of preservation of the parenchyma of the gland that controls the absorption of food from the intestine. A disease process that disorganizes a large part of the secretory acini causes large losses of fat and nitrogen from the intestine. If only a part, small but healthy, is preserved, absorption may remain good. Thus maintenance of functional activity in the gland probably depends upon an internal secretion just as it does in the thyroid or parathyroid or pituitary gland.

The internal secretion of the pancreas is as important as the more obviously essential external secretion, and is the regulator of the absorptive activities of the intestine.

*Summary*—We have attempted to analyze in a series of cases of obstructive jaundice the individual clinical symptoms, and have essayed to arrive at a proper diagnosis before operation. In so doing we have utilized the assistance offered by analysis of the duodenal contents and of the stools, and have correlated the clinical facts with the laboratory data. By ascertaining the condition of patency of both biliary and pancreatic systems and by determining the functional activity of the pancreas we have had valuable additional data upon which to construct a more accurate diagnostic opinion. Full details of the technical procedure of duodenal contents examination and its clinical application can be obtained in the following articles.

Experiences with Duodenal and Stool Ferments in Health and Disease, Eighth International Congress of Applied Chemistry, vol. xix, page 73

Chemical Examination of Duodenal Contents as a Means of Diagnosis in Conditions of Jaundice, *Journal of the American Medical Association*, 1915, lxiv, page 565

New Growths Involving the Terminal Bile and Pancreatic Ducts, *Journal of the American Medical Association*, 1914, cxlviii, page 839

Studies in Pancreatic Disease, *Archives of Internal Medicine*, 1915, xv, page 581

## CLINIC OF DR S PHILIP GOODHART

### MONTEFIORE HOSPITAL

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## THE PRIMARY MYOPATHIES AND THEIR ENDOCRINE RELATIONSHIP

Clinical Findings    Familial Tendency    Distribution of Muscles Affected.    Changes in Electric Reactions.    Different Types of Muscular Dystrophy, Characteristic Features of Each.    Earliest Manifestations.    Pathologic Processes in Muscles    Changes in Other Tissues.    Illustrative Cases.    Discussion of Endocrine Relationship and Possibilities of Therapy

IN choosing the subject for today's lecture I have made a careful selection of cases for demonstration with a view to impressing upon you not only the clinical features of muscular dystrophy as we see it in these advanced cases, but of the possibility of preventing such an outcome by early endocrine and other therapy

**Analysis of the Disease**—The term "idiopathic muscular atrophy" has long been used to designate a group of cases which, although for a time erroneously allied in pathology with muscle atrophies due to spinal cord lesions, are now known to be quite independent and different from such atrophies. The group of cases we have under consideration today is known by the comprehensive designation "muscular dystrophy," and belong to the class of primary myopathies. The first true cases of this type, probably, were described by Charles Bell in 1830.

Clinically, they are characterized by atrophy and pseudo-hypertrophy of certain groups of muscles, but their grouping differs from that occurring in progressive muscular atrophy. The latter disease, analogous symptomatically to chronic poliomyelitis, is due to degeneration of the anterior horn cells of the

cord In the pathology of the dystrophies lesions of the cerebral and peripheral nervous system are never discovered as part of the definite findings

The disease is essentially a familial abiotrophic manifestation occurring in several members of the same family, of the same or of a subsequent generation The disease seems to be transmitted through the maternal influence The disease is more apt to develop in the male members of a family than in the female You will see the great predominance of male patients in the cases presented to you today, and also the frequency with which brothers are affected The female members of a family themselves usually escape, although they may transmit the disease to their sons Gowers reports a case of transmission by the female side to the third generation

The general obtrusive clinical features of dystrophies, as distinguished from the progressive muscular atrophies of central nervous origin, are the distinctive distribution of muscles affected and the apparent enlargement of some of the diseased muscles Furthermore, in these diseased muscles the changes in electric reaction are such as result from quantitative loss of muscle tissue, and hence are purely quantitative, while in progressive muscular atrophy qualitative changes, with change of reaction formula, occur In the dystrophies, the axial, girdle, pelvic, and trunk muscles are affected, while in spinal atrophies the peripheral or distal groups, the extremities, are primarily involved Fibrillary twitchings are absent in the muscles affected in muscular dystrophies, since the trophic center, the nerve-cell of the anterior horn, is intact

Several varieties of muscular dystrophy are recognized according to the onset of the disease, with especial reference to the muscles affected The cases I am presenting to you illustrate these several types It should be remembered, however, that, in reality, these groups merge into each other, and it is most common to find mixed types Three types are commonly recognized the facioscapulohumeral type, or Landouzy-Derjane type, or the *atrophie musculaire progressive de l'enfance* of Duchenne, the juvenile form of Erb, and the pseudohypertrophic

type of Duchenne. In the facioscapulohumeral type the atrophy begins in the muscles of the face, and may be confined to the face symmetrically for some time before other muscles are involved. This type usually begins in early life, most often in infancy. The atrophic musculature soon gives the face the typical expression called "the myopathic face." Three of the patients whom I shall show you today (Cases V, VI, and VII) illustrate this. The expression appears apathetic, the forehead is not wrinkled, the nasolabial folds are absent, the lips appear large, thickened, the mouth pointed or snout like on the lateral aspect. The mouth cannot be elevated, as a result of which the so-called transverse smile is seen in repose. Puckering of the lips is no longer possible. The eyes cannot be completely closed. The affection of the orbicularis palpebrarum and oris, so often the first muscles attacked, gives the peculiar spiritual facial expression, the so-called *facies beati*. The expression of the patient may suggest mental defect, but the intellect is not impaired, as you may see upon interrogation of the patients to be presented today.

The next groups of muscles to be affected are usually those of the upper limbs, especially about the shoulders and upper arms, the shoulder girdle groups. This sequence of muscle involvement explains why this is called the facioscapulohumeral type. The supra- and infraspinati and subscapularis usually escape. In the pure form there is only atrophy and no hypertrophy. In this type, as in that described by Erb as the juvenile type of progressive muscular dystrophy, the sexes are about equally affected. The muscles affected most early are the serratus magnus, the trapezius, and the rhomboidei. The winged scapulae, so often seen, are due to atrophy of the rhomboidei and serrati (Case I). The involvement of the lower limbs may occur at approximately the same time, but it is usually later than that of the upper. Invariably the proximal groups alone are at first affected, and it is only very late, if at all, that the distal ones become involved.

The trunk muscles, including those of the abdomen, may be early involved, with a resulting lordosis so often observed in this

disease, and as is shown in three of the cases presented That the osseous changes are not due to mechanical conditions I shall point out to you later It is principally the atrophy of the trunk muscles and extensors of the hips and knees that makes these patients "climb up upon themselves," so to speak, when assuming the upright from a prone position, as will be illustrated to you by our patients, for I shall ask those affected in this way to lie upon their backs, and you will observe the characteristic manner in which they reach the upright position, first kneeling, then raising one knee, then with the hand upon the knee working upward in a manner as though really climbing upon their own leg and thigh and trunk Thus, with the characteristic waddling gait and lordotic pose, makes the clinical picture at once clear to the observer In attempting to arise the patient rotates the whole body by means of pressure with the arms to the ground, thus getting over on one side, he then flexes the hips, drawing up the knees under the abdomen, and is able, by rotating the trunk around the knees as a lever, "to get on all fours", he then extends his knees by throwing his head down between the arms, with the knees extended, he keeps the feet fixed and then works back on his hands, places one hand and then the other from the ground to the knee, and he now extends his hip by transferring each hand in turn to a higher level on the thigh, and then shifts his center of gravity backward by suddenly throwing the shoulders backward

It will be observed further that the deformity of the spine is peculiar and changes its curves in the standing and sitting postures When the patient stands one sees marked lordosis with lumbar concavity and a high degree of compensatory convexity of the upper dorsal and lower cervical vertebræ In the sitting position these curves disappear, they are transformed to a single kyphotic curve with concavity forward

In some of our cases you will observe contractures of some muscles giving rise to forms of talipes, especially talipes equinus due to secondary contractures of the hypertrophied calf muscles which contain an abnormal quantity of fibrous connective tissue In the two forms, the juvenile type of Erb and the Landouzy-

Dejerine type when pure, there are no hypertrophies, although a peculiar pseudo-enlargement, really due at least in part to adjacent atrophy, is often seen in the central portion, especially of the biceps, deltoids, and calf muscles

The juvenile or scapulohumeral type was first described by Erb of Heidelberg. This does not differ from the Landouzy-Dejerine type except that it often appears later in life and the face is not involved. In the juvenile form the biceps, triceps, and supinator longus are the first usually affected, soon the pectoralis major and latissimus dorsi become involved, and the serratus magnus is often paralyzed, though the deltoids and supra and infraspinati are frequently intact, thus allowing the scapulae to stand out prominently at their posterior border and lower angle when the patient extends his arms straight out in front of him (Case I). The trapezius is often affected in its entire length, including the superior clavicular portion, as a result of which the normal slope of the neck to the shoulders is changed, giving a characteristic attitude of myopathies. In some cases the sternocleidomastoids are affected, in fact, often being congenitally absent in the aberrant type of myopathy associated with muscular dystrophy, and this condition is known as amyotonia atrophica, as illustrated by the case of the woman we will examine today (Case II).

The true pseudohypertrophic form of dystrophy is essentially a disease of childhood. It is familial and boys are more often affected than girls. Cases V, VI, VII, IX, which I shall demonstrate today, are examples. Certain muscles are, as a rule, apparently enlarged throughout the course of the disease. When the patients are seen early the calves, hips, and buttocks appear unusually large, although the arm and trunk muscles may be of normal size and contour. As was evidenced in our cases, the first sign is usually some difficulty in walking. The child is observed to stumble frequently and climbing stairs is difficult. In contrast with the weakness there is an apparent enlargement of the muscle groups. There is often atrophy of some and hypertrophy of other muscles. The muscles which tend to show enlargement of tissue are the calf muscles, the gastrocnemius and



soleus They assume a peculiar shape, the posterior border of the calf appearing elliptic with prominent convexity over the middle of the calf, and the muscle tissue, or rather its modification, has a most peculiar hard feel, as you can easily verify by examining the patients before you From the weakness of these muscles, as demonstrated by the patients' inability to stand upon their toes, as well as by the peculiar feel and shape, you can see that the hypertrophy is not a true hypertrophy of muscle tissue The process is indeed pathologic, as we shall more clearly see later The pathologic process resulting in additional tissue and appearing as pseudohypertrophy is further seen in the glutei The flexors and adductors of the hip and flexors of the knee are usually atrophic Of course, the apparently large muscles eventually lose their shape and fulness, but the peculiar hard feel and relative enlargement can be demonstrated throughout the course of the disease The erector spinæ is sometimes hypertrophied, but in my personal experience it has usually been atrophic

Of the shoulder girdle group, the deltoid has especially proved to be the seat of early pseudohypertrophy, as, to a lesser extent, have the supra- and infraspinati As we may observe in our cases, the deltoid long remains as a peculiar hard mass In the forearm, as we see here, the triceps tends to hypertrophy, showing a convex outline, while the biceps is practically gone Further, among the atrophic muscles are the lower portion of the pectoralis major and the latissimus dorsi The loss of pectoralis major we will demonstrate by having the patient put both arms out horizontally in front of his body, upon pressing the hands together the upper portion of the muscle alone is seen to contract

Generally speaking, the clinical picture of progressive muscular dystrophy is so characteristic that one should have no difficulty in making the diagnosis, even in very early cases The conspicuous features are characteristic muscle group involvement, pseudohypertrophy and weakness, atrophy, quantitative changes in electric reactions, diminution of deep reflexes corresponding to the amount of tissue lost, and absence of all sensory changes and of fibrillary twitching Furthermore, we

may add the association of other tissues involved, especially bones, hair, skin, pigment and fat deposits, and characteristic metabolic findings. The osseous changes, as demonstrated by roentgenographic examination, are seemingly constant.

The pathologic changes in the muscles are interesting. The muscles are found, postmortem either to be in an advanced stage of atrophy or if they have been enlarged, they are diminished to about the normal size. In color the muscle is paler than normal. In extreme cases, on cross-section in the gross, they appear as a fatty tumor without trace of muscle tissue. Microscopically the muscle fibers, when the process is not too far advanced, are found diminished in size and number, and on cross-section are found to have lost their normal contour. They may be separated by fat cells and bands of fibrous tissue. The relative amount of fat and fibrous tissue differs in the various muscles. In the early process the deposition of fat in masses suggests fatty deposits in other parts of the body.

The so-called pseudohypertrophy of certain muscle groups is characteristic of this disease. Most observers speak of the hypertrophy as in part a true muscle-fiber enlargement similar to physiologic hypertrophy. This is an error. A true hypertrophy of muscle consists in an increase in the number of normal muscle-fibers and in the bulk of sarcoplasm present in the muscle. These are not the findings in muscular dystrophy. Physiologically hypertrophied muscle does not show the splitting and loss of angular contour of the fibers, the proliferation of connective tissue and fat deposit shown by the tissue from muscular atrophy cases. Spiller thought that the many nuclei present in muscle from dystrophy cases indicated true growth but nevertheless admitted that the other histologic abnormalities were the same as originally described by Erb of Heidelberg and thus of a degenerative nature. On the whole, the process is one of degeneration. Its cause we will speak of further on after the demonstration of our cases.

The following cases are typical of the several types with their variable features which I shall demonstrate in each, showing the cases in the order of their severity.

CASE I, a boy eleven years of age, had one sister who was also affected with muscular dystrophy. Four years previous to his admission to this hospital he was operated upon for cataracts of both eyes. His present illness began at four years of age, with distinct progressive weakness in all the muscles of the



Fig 44 —Case I. Winged scapulae.  
Characteristic pose in assuming upright position

body. There is at present general muscular wasting and weakness, with the exception of the calf muscles, which are in a condition of pseudohypertrophy. When lying on the floor the patient assumes the erect position in a characteristic manner by rising on one knee, extending the other leg, pulling himself up on that, and then dragging up the other leg. There is a myotonic reaction in the tongue, thenar and hypothenar eminences, and the deep reflexes are but feebly elicited. A partial myotonic reaction is found in this and in the following case. The muscles of the tongue, thenar and hypothenar eminences are, therefore, affected. The myotonic action to be observed in these two cases can be demonstrated by percussion over the

muscles thus. When I tap the muscle over the thenar eminence you will notice a slow, tonic, protracted contraction follows. The muscle stands out like a tumor, again, upon repeating the mechanical stimulus, it shows depressions and ridges at the points struck. The mechanical excitability of the nerves is not increased. Upon percussing the protruded tongue you observe the same myotonic phenomenon. When walking the patient has a characteristic steppage gait. On appropriate movements

there are typical winged scapulae. The facies is of the myopathic type and there is very little fatty tissue. You will observe the abnormal growth of hair on the extensor surfaces of the upper extremities just above and below the elbow. Marked cyanosis is present in the peripheral portions of all four extremities and is only slightly influenced by posture, the hands remaining distinctly cyanosed even when elevated. The Wassermann reaction is negative. The roentgenographic examination of the skull and long bones was essentially negative.

CASE II is a woman, forty-three years of age. This case is really a mixed type, an amyotonia atrophica, combined with progressive muscular dystrophy. One brother died in his forty-fifth year of progressive muscular dystrophy. In our patient the disease began in the thirty-eighth year, with weakness in the lower extremities and also in the upper, but in lesser degree. Motor paresis in the neck muscles developed later. At present the facies is characteristic of primary myopathy, motor power is markedly diminished, there is intense cyanosis of the feet,



Fig. 45—Case II. Only case of muscular dystrophy in a female in the series associated with myotonia atrophica.

the volume of musculature is lost throughout the body, with far greater relative diminution of function, the gait is slow and hesitating, with broad base, there is wasting of muscles of neck and shoulders, the sternocleidomastoids are atrophic, there is myotonic reaction in muscles of tongue and right thenar and hypothenar eminences. The patient is unable to raise herself on the chair without assistance, and she has a low monotonous speech. The roentgenogram shows small spots of bone absorption scattered throughout the upper portion of the cranium. There is a faint shadow, about 5 by 7 mm, situated slightly

above and 3.5 cm posterior to the tip of the posterior clinoid process. This shadow suggests the pineal gland.

CASE III, a man forty-two years of age, has two brothers known to have muscular dystrophy. The patient lived under unhygienic conditions, his work exposing him to metallic dust of lead, brass, antimony, etc. The onset, which began in his



Fig. 46—Case III. Exophthalmos, hypertrophy of calves, and deposits of fat

twenty-sixth year, was gradual, there was progressive weakness in the right arm, extending to the left, then involving both lower extremities. There is marked exophthalmos and dilated pupils. The patient cannot voluntarily assume a sitting posture, but maintains it when assisted. The head is flexed and rotated to the right. There is marked atrophy of the sternocleidomastoids, trapezi, and muscles of the forearm. The deep

reflexes are absent, the knee jerks diminished. The characteristics exhibited in this case are contrasted pseudohypertrophy and weakness of function of the calf muscles. The muscle tissue seems to be replaced almost entirely by fat. The Wassermann reaction is negative. The roentgenograms show very marked bone rarefaction in the skull, evidently in the tabula interna simulating strongly the convolutions of the brain. The extremities show moderate diffuse bone rarefaction somewhat more marked in the lower. In both tibiae there is evidence of very advanced localized bone absorption running in the form of two narrow strips throughout the upper half of the diaphysis, suggesting cavity formation.



Fig. 47—Case IV. Wasp-like contour of body.

**CASE IV** a man forty-eight years of age, has two brothers who are affected with primary myopathy. The onset of this patient's illness was in his thirtieth year, with weakness in both upper and lower extremities. He is able to move about only in a wheel chair, and has difficulty in assuming a sitting position. There is flexion of both thighs and knees and contraction of the hamstring muscles. Extension of legs is limited to 130 degrees. His body is of wasp-like contour, facies myopathica, and the calf muscles are weak and have the characteristic sclerotic feel. Pseudohypertrophy is present. There is marked wasting of the general musculature. The deep reflexes cannot be elicited because of atrophy. Electric examination shows quantitative changes in the affected muscles. The skin is cold and clammy, the feet cold and cyanotic, and there are

trophic changes in the nails. The pulse is slow and of low tension. Roentgenograms show several small irregular spots of bone absorption scattered throughout the parietals and frontals. There is an irregular shadow, about 0.5 to 1 cm. on the level of and 4 cm. posterior to the tip of the posterior clinoid process (pineal body?). Evidence of bone absorption of the posterior

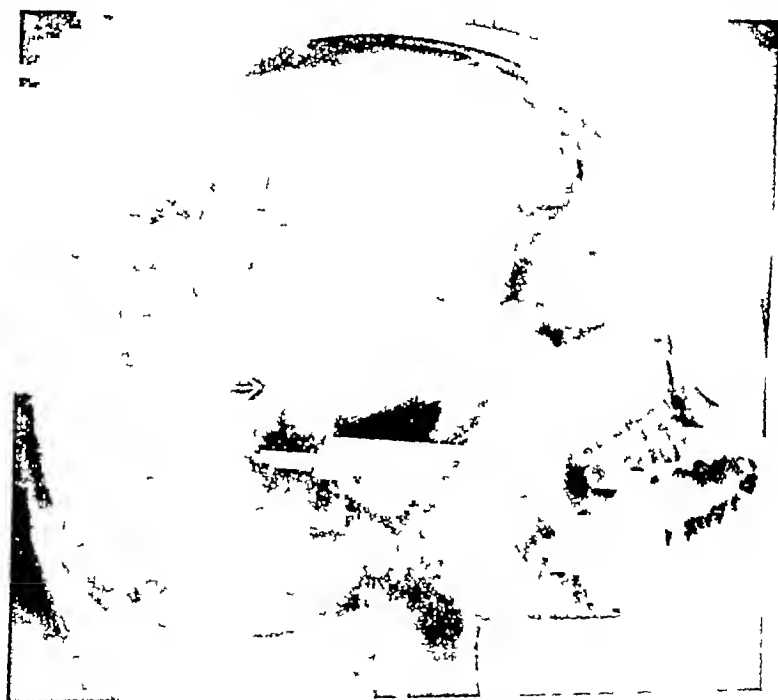


Fig. 48—Case IV. Shadow of pineal body, small irregular spots of bone absorption throughout parietal and frontal bones.

clinoid process is present. The sella turcica is not enlarged. There is marked diffuse bone atrophy in the upper extremities. In some places differentiation between compacta and spongiosa has entirely disappeared. There is a moderate amount of diffuse atrophy of all bones of the lower extremity, including tarsal bones.

CASE V, a young man nineteen years of age, has two brothers

who are affected with progressive muscular dystrophy. The patient has an extra digit on all four extremities (congenital deformity). When he was three years of age he began to exhibit progressive weakness in the order named, of the lower extremities upper extremities back, and facial musculature. The calf muscles show the usual pseudohypertrophy with the characteristic sclerotic feel. The whole skeletal structure ap-

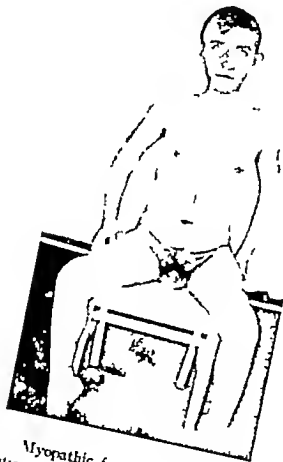


Fig 49—Case V. Myopathic facies. Unusual growth of hair about the hips. Marked diminution in length of long bones. Whole skeletal structure stunted. Underdevelopment of genitalia.

pears stunted the long bones between the knees and ankles are abnormally short and there is a peculiar distribution of the hairs about the individual hairs being abnormally long especially about the groins and thigh anteriorly. The roentgenograms show underdevelopment of the long bones and absorption of osseous tissue.

CASE VI eighteen years of age has a very significant family



history His father is an epileptic, he has two brothers affected with muscular dystrophy, and one maternal aunt is insane The onset in this patient began in his fifth year with generalized muscular weakness and slowly progressive wasting The calf muscles show typical pseudohypertrophy, and the muscles, orbicularis oris and palpebrarum, are atrophic The trunk deformities are in large part due to muscle wasting The hair is



Fig 50 —Case VI Skeletal deformities, myopathic facies, talipes equinus

strikingly long and abnormally distributed on the body, the scalp hair is very dry and brittle There are trophic ulcers on the fingers and toes The roentgenograms show marked, diffuse rarefaction of all bones examined They are abnormally thin and underdeveloped

CASE VII, a boy fifteen years of age, displays profound muscular weakness with contractures involving almost the entire musculature of the limbs and trunk The sternocleido-

mastoids are atrophied and there is extreme distortion of the trunk. This case represents an advanced muscular degeneration. The facial muscles on both sides are involved in the typical myopathic loss of function on effort. The exophthal-



Fig 51—Case VII Exophthalmos, myopathic facies skeletal deformities extreme muscular atrophy

mos is emphasized by the partial wasting of the orbicularis palpebrarum. There is marked dryness of the skin on the abdomen and a deposition of brown pigment. The teeth are wide apart and there is macroglossia. The roentgenograms



Fig 52—Case VIII Extreme skeletal deformities, marked general atrophy peculiar distribution of hair about buttocks and thighs.

show marked underdevelopment and rarefaction of all bones examined most advanced in the carpus and tarsus.

CASE VIII a young man nineteen years of age has one brother affected with muscular dystrophy. In his third year our patient's manner of gaining the erect position typical of

muscular dystrophy, was observed. He was never able to run or to climb stairs. There is marked wasting of all muscles of the body and contractures in the hamstring and calf muscles. The enlargement of the calf muscles and the peculiar sclerotic feel are in contrast to the marked general atrophy elsewhere. The skin is peculiarly dry, with diffuse areas of brownish pigmentation, and a prolific, long hairy growth about the pelvis and thighs. The cyanosis of the lower extremities in the distal



Fig. 53—Case IX. Hypertrophy of calf muscles, acromegalic features, general massive contour of head and face.

portions is marked and there is a tendency of the soft parts to ulceration. Roentgenograms show atrophy of all bones examined. The lower portions of the ulnæ and radii are abnormally thin from underdevelopment.

CASE IX, a boy fourteen years of age, has a family history containing no element relevant to the patient's condition. The initial symptoms bearing on the development of the muscular dystrophy date from his third year. There is a history of gradual

weakness, beginning in the lower extremities, progressively involving the girdle, facial, and shoulder musculature. Pseudo hypertrophy and atrophy have finally reached a very high degree. There is also, in part secondary to the marked involvement of the trunk muscles, extensive kyphoscoliosis from the sixth dorsal to the midsacral region. The general massive bony contour of the head and face, and especially the marked prognathic lower maxilla, are decidedly of the acromegalic cast. The sexual development, in contradistinction to the other cases reported



Fig 54—Case IX. Macroglossia.

shows abnormally advanced maturity of growth. There is marked macroglossia, the tongue on protrusion being really huge. There is excessive growth of hair over the entire body. Roentgenographic study of the skeletal structure examined shows the usual underdevelopment of the long bones. Those of the skull, especially the lower jaw present markedly acromegalic features. CASE X, a boy fourteen years of age has one brother with muscular dystrophy, but the family history as to nervous mental, and otherwise hereditary influences is negative. The patient's

illness was first observed when he was seven years of age, the symptoms were weakness of the muscles of the lower extremities. The involvement of the upper extremities began about the age of twelve, that is, some five years following the involvement of the legs. I would call your attention at this point to the frequent observation made in these cases, namely, that the evidence of some motor defect has been that of difficulty in ascending and descending stairs.



Fig 55—Marked atrophy. Abnormally long phalanges, skeletal malformation, obliteration of nasolateral folds, characteristic fulness about the mouth.

Our examination of this boy shows a bedridden patient in a recumbent posture. There is present the familiar group involvement affecting the girdle, shoulder, and hip musculature, and peripheral groups remaining comparatively little affected. The electric reactions and deep reflexes again show only quantitative electric reduction, and the reflexes diminished or absent to the extent of the atrophy. You observe a very marked kyphoscoliosis and a general relaxation of the ligaments and skeletal joint structures. The atrophy is extreme. Both lower extremities are permanently flexed at the knee-joints, due to secondary contractures,

of mechanical origin, of the ham strings. These contractures are not of the character, of course, of spastic changes in the central nervous system. The chest shows marked asymmetry. The lower ribs on the right side are almost in contact with the pelvis so great is the general relaxation and muscular atrophy. There is complete atrophy of the deltoids, biceps, and triceps. Only the muscles of the calves show the relative pseudohypertrophy and



Fig. 56—Showing underdevelopment of humerus.

the characteristic sclerotic feel. The facies is typically myopathic. The lips appear full and pointed and the facial weakness is evident from the facial appearance and absence of the normal folds and the patient's inability to actively execute the common movements such as closing the eyes tightly, whistling, blowing, etc. The skeleton presents some characteristic abnormalities, unusual length of long bones especially the phalanges, and very marked underdevelopment in circumference, as shown

in the roentgenograms The hair is dry and rough to a remarkable degree, the hair of the head, to the examiner's touch, feel-



Fig 57 —Characteristic underdevelopment of long bone

ing like a hard brush Hirsutes are abundant on the extensor surfaces of the legs

Our conception of progressive muscular dystrophy has undergone a great change within very recent times As in the case of

other pathologic manifestations of muscle structure and function, such as myasthenia gravis psuedoparalytica, tetany, myotonia congenita, etc., we are beginning to look upon these phenomena as but part of more general disturbances of the organism with pathologic evidence in other tissues as well. The basis for the more generalized manifestations we now recognize in the pathogenesis of endocrine dysfunction. While admitting the restraint necessary in accepting a great deal that has been claimed for endocrine influence in general, there seems to be no question but the glands of internal secretion, namely, the thyroid, pituitary, gonads, thymus, parathyroids, and adrenals, play a most important etiologic rôle in the production of the disturbance of bodily functions. Certain syndromes and their identification with perverted function of certain endocrine glands are, as you know, definitely established. I need only mention, for example, the group of symptoms associated with pituitary and thyroid dysfunction. In practically every one of the cases of muscular dystrophy before you distinct evidence of endocrine involvement is to be found. We have but to refer to the physical examinations in each case, including the metabolic investigations and roentgenologic findings. Let me refresh your memory for a moment in regard to the symptoms produced by dysfunction of the hypophysis. You will recall that hypopituitarism, occurring before pubescence, manifests itself clinically by a diminution of bodily hair, obesity, underdevelopment of the genitalia, feminine contour of the body in the male, and amenorrhea in the female. If the posterior lobe is especially involved the prominent symptoms are increased sugar tolerance, adiposity, and low blood pressure. Again, hyperactivity before puberty frequently induces a precocious degree of sexual development, overgrowth of bodily hair, and excessive skeletal growth. Overactivity of the posterior lobe usually induces decreased sugar tolerance and high arterial pressure. Our cases embody some of the important symptoms enumerated.

Since the subject under our consideration today deals particularly with disturbances of muscle tissue and function, let me call your attention to the relation of endocrine activity to that struc-



ture Data are fast accumulating to show that muscular dystrophies may have their origin in the disturbed activity of the organs of internal secretion The therapeutic importance of the establishment of this etiology is at once apparent Indeed, throughout the literature examples are beginning to appear indicating that endocrine therapy has been followed by favorable results in many cases of apparent primary muscle disease In our series of cases, as in others which have been published, it is impossible to state which one of the several endocrine glands is primarily at fault In our series roentgenographic studies were made with a view of determining involvement of the pineal gland In only two cases were we able to find definite shadows which could be ascribed to that gland That these shadows really represent pathologic conditions in the pineal body is questionable, though some authors, calling attention to the muscular weakness observed in pineal disease and to its probable involvement in some cases, speak of the possible pineal origin of certain cases of muscular dystrophy On the other hand, the thyroid, the hypophysis, the adrenal, and the gonads are represented in symptoms associated with cases of the primary myopathies It is not unlikely that the muscular dystrophies, and perhaps other so-called primary myopathies, are really but symptom complexes caused by dysfunction, not of any one, but of various endocrine glands separately or coincidentally affected We must remember in this connection that symptoms which represent dysfunction of one of the glands of internal secretion may be identical with symptoms of the disturbance of another of the ductless glands For example, retardation of growth, defective osseous formation, and adiposity may result from dysfunction of the thyroid, the pituitary, or the gonads

The clinical and pathologic evidence, and now studies in metabolism as carried on here at the Montefiore Hospital on the cases presented today, point most strongly to endocrine influence Studies of these cases, with a view toward comparing the results with those found in others of unquestionable endocrine origin, were carried on by Dr Janney, Mr Isaacson, and myself, and our findings add data confirmatory to that of other observers, and

strongly suggest the influence of the endocrine glands. Furthermore, in view of our findings of definite pathologic changes in structures other than the muscles, especially the skeletal, we may reasonably conclude that the muscular anomalies are but part of a more general pathologic participation. In all of our cases we found symptoms of disturbance in the physiologic chemistry of the organism identical with those recognized in dysfunction of certain of the organs of internal secretion, further, we found clinical evidence in nearly all of our cases of changes in trophism, of hair, skin, nails, etc., anomalous distribution of hair in some, pigment and fat deposits, local and general, and characteristic osseous changes in others. Roentgenographic studies made in each case showed, in all but one, rarefaction of the skull and long bones with underdevelopment and peculiar cavity formation, in one there are distinct acromegalic features. The metabolic changes are essentially those found in disease of undisputed endocrine origin, such as Addison's disease, hypopituitarism, myxedema, and after experimental removal of the thyroid or adrenal glands in animals.

The metabolic experimental findings of Janney, Isaacson, and myself (reported in the *Archives of Internal Medicine*, February, 1918) in 9 of the cases here presented to you are briefly as follows. A marked decrease in the preformed creatinin, abnormal presence of creatin in the urine, low values of creatinin in the blood, a normal amount of creatin in the blood, hypoglycemia, and delayed glucose utilization. What do these findings suggest? Hypoglycemia, that is, abnormally small amounts of sugar in the blood, is observed in conditions known to be due to dysfunction of certain of the endocrine glands, e. g., in myxedema and cretinism. In the latter, creatin has been found in the urine. Creatin, as you know, is intimately associated with muscle structure and function, and it has been determined that there is a relationship between endocrine function and the excretion of creatin and creatinin. Creatin is not normally present in the urine. The amount of creatinin in urine may be regarded as a measure of muscular efficiency. In exophthalmic goiter, myotonia congenita, myasthenia gravis, and in muscular dystrophy

the excretion of creatinin is markedly diminished. The suprarenal glands doubtless play a rôle in the metabolism of muscle as shown by their influence on creatin excretion. In rabbits a lesion of the suprarenals causes a more or less marked diminution of the creatinin production. Injections of adrenalin increase the excretion of creatinin. Hypophysis extract, subcutaneously injected, augments the daily creatinin output, especially when that of the posterior lobe is injected. Thyroid extract has no effect on the creatin and creatinin output, as determined by animal experimentation. Removal of the ovaries does not alter the creatinin production, but the animal no longer reacts with increased creatinin excretion after subcutaneous injection of adrenalin or hypophysis extract. Thus we see the direct bearing upon muscle metabolism of the endocrine secretions.

In this hospital Janney has found a delay in the utilization of carbohydrate, as shown by a study of the sugar curve of the blood in cases of cretinism and exophthalmic goiter. It is, indeed, not improbable that the pathogenesis of at least some of the primary myopathies lies in defects of carbohydrate metabolism. We know that the presence of creatin in the urine is a sign of destruction of muscle tissue and that creatin immediately disappears from the urine when carbohydrate is ingested. It would appear that disturbed carbohydrate metabolism is the basis of the metabolic changes found in muscular dystrophy, and also that in this disease a degenerative process, as a result of disturbed carbohydrate metabolism, is undergone by the muscles not receiving their normal supply of pabulum, and, as a result, creatin appears in the urine. The process appears to be primarily one of endocrine dysfunction with secondary disturbances of metabolism.

Let us consider further this influence of some of the endocrine organs upon muscle function. The action of the suprarenal secretion on muscle activity is striking and strongly suggests the influence of that endocrine gland in the muscle diseases. The most important signs of suprarenal insufficiency are muscular asthenia and muscle hypotonia, other symptoms, such as melanoderma, gastro-intestinal derangements, and celiac pain being less usual. Opoththerapy, especially administration of suprarenal gland, fre-

quently very favorably influences the muscle fatigability and the asthenia. Furthermore, there seems to be a direct relationship between the established symptoms of suprarenal insufficiency and myasthenia gravis. The latter is characterized by paroxysmal fatigability, next asthenia, and finally permanent paresis of the affected muscles. The muscles show the characteristic myasthenic reactions. In addition, hypotension of the vascular system, shown by lowered blood pressure, is present. The manifestations of suprarenal insufficiency differ from those seen in myasthenia by the involvement of bulbar centers which are affected in the latter, and by generalization of the muscular weakness in deficient adrenal secretion. Not infrequently, however, alteration of the suprarenals, found in myasthenia, with pigmentations and hypotension, is favorably influenced by opotherapy. In one of my cases in private practice the symptoms of myasthenia gravis were for a time markedly influenced by opotherapy (thymus), especially large doses. I recall just now the favorable reports throughout the literature of the several endocrine hormones in muscle affections. Hypophysis therapy is reported to have yielded favorable results in affections of the myocardium, both in the course of certain acute intoxications and infections, but especially in some chronic conditions of myocarditis, and finally in tachycardia. P. Carnot (Paris, 1911) speaks of such cases, and the same observer has seen improvement from thymic therapy in cases of muscular dystrophy. The literature contains innumerable references to cases of various types of muscular affections favorably influenced by endocrine therapy.

A review of the literature discloses many references and reports of cases to show that the phenomena of myasthenia gravis, with its peculiar and characteristic muscle disturbance, has etiologic relationship with perverted endocrine activity. As in other phenomena of muscle metabolic derangement, no one gland can be positively identified. Primarily, there is much to suggest thymic influence, its pathologic activity causing the entrance of products with a toxic action into the circulation. Myasthenia associated with exophthalmos and pigmentation of the skin, as seen in adrenal insufficiency, etc., repeatedly observed and re-

ported, suggests pluriglandular activity. Just how the suprarenal secretion influences muscle structure we do not know definitely. The suprarenals are credited with the property of destroying or neutralizing toxic substances which originate with contraction of the muscles. The suprarenal cortex secretes lecithin, which has a myotonic property and which contains adrenalin. The suprarenal parenchyma secretes adrenalin which has the property of raising blood-pressure and a muscular tonic action. Contact of adrenalin with striped muscle tissue destroys its efficiency, especially when the muscle is fatigued. Greater muscular efforts lead to increased production of adrenalin. The muscle requires adrenalin for its contraction. In suprarenal insufficiency the myotonic element is lacking. The relationship, therefore, between muscle tone and activity and this endocrine influence is apparent.

On the other hand, the influence of another endocrine gland, the pituitary, on unstriped muscle-fiber is known to you, and gives further substantiation of endocrine importance in determining muscle activity and perhaps muscle integrity and development. Just as skeletal growth is influenced by pituitary activity, so doubtless is muscle structure. We are all familiar with the striking stimulating effect of pituitary extract upon the muscles of the uterus, bladder, and small intestine. It is established that the contractions of the muscles under the influence of pituitary extract are prolonged in time, but are of less frequency. This peculiar prolonging of the contraction suggests the perhaps analogous prolonging of the contraction as seen in certain muscle diseases, and as demonstrated in some of our cases today, and as seen in myotonia congenita, or Thomsen's disease, and possibly tetany. In the latter thyroid or parathyroid influence can scarcely be disputed. Animal thyroid extirpation experiments, as well as partial removal in humans, has resulted in tetany.

Functional disturbances of one of the endocrine glands are apt to be associated with similar disturbances in the domain of the other glands of internal secretion, so that it is sometimes difficult to identify positively the primarily diseased organ. I would call your attention to the existence of an apparently close

anatomic and physiologic connection between many endocrine glands as shown in the clinical picture by the onset of symptoms, in disease of one endocrine gland which can be referred to functional disturbances on the part of another, or several other glands of internal secretion. The variegated interrelations between the endocrine glands are well established at the present state of our knowledge, and isolated affections of individual organs of this group are now known to occur much less frequently than was formerly believed to be the case.

The term "pluriglandular insufficiency," of French writers (Claude and Gougerot, 1907), is applied to a symptom complex based upon the universal atrophy and functional insufficiency of a series of endocrine organs. It must be kept in mind, however, that functional disturbances of an internally secreting organ, in the positive or negative sense (meaning increased or diminished function), are not necessarily followed by analogous changes in the activity of the other organs, so that, as a matter of fact, the hyperfunction of some endocrine organs is found to be associated with the hypofunction of others, and vice versa. For example, cases of polyglandular insufficiency have been described combined with hyperpituitarism, and others with hypopituitarism.

In persons with an apparently congenital inferiority of the endocrine organs symptoms pointing to a diminished function of several internal secreting glands, in a great variety of combinations, make their appearance at the time of puberty or later, under the influence of various injurious factors, such as infectious diseases, especially tuberculosis and syphilis, abuse of alcohol, etc. The most clearly outlined of these multiglandular affections is the *thyreo-testiculo-hypophyseal-suprarenal syndrome*, in which deficiency symptoms on the part of the thyroid gland (apathy, muscular weakness, loss of hair, changes of the skin and teeth) are combined with signs of diminished function of the sex glands, and with symptoms referable to disease of the hypophysis and the suprarenals. Other cases present the *thyreosuprarenal*, *thyreo hypophyseal*, or *hypophyseosuprarenal* type.

Up to now our positive knowledge of the pathogenesis of the primary myopathies, particularly the dystrophies, is confined to

the nutritional disturbances found in the substance of muscle, and are apparently independent of changes in the central or peripheral nervous system. The nutritional changes, as we have shown, are not confined to muscle tissue, and thus indicate more general, though selective, metabolic changes. In addition to the muscle pathology we have found articular, osseous, and skin changes.

In view of the relations of the endocrine organs with the sympathetic and autonomous nervous systems, as well as their interrelations, it is not unlikely that any disturbance of one endocrine gland disturbs the equilibrium of the entire system. Certain apparent exceptions to the established rule of endocrine activity awakens the suggestion that at least some of the endocrine glands excrete two distinct and antagonistic hormones.

From the therapeutic standpoint it seems perfectly feasible to consider, first, treatment of the mother during the period of gestation with that gland which, after careful observation and study, is apparently the seat of dysfunction, for muscular dystrophy, as we have seen, is a familial defect. One male offspring, as we know, afflicted with the disease is but a herald of successive members of the family. Again, in very early life were selective endocrine therapy studiously carried out we might find the element that appears to be a factor, or perhaps *the* factor, in regulating the defective metabolism. This is but a suggestion, although, in view of what has been presented to you today, I feel justified in urging this method of therapy in a disease which is so far progressive and fatal.

Insufficiency of gonadal secretion in the male may be observed at any age. The majority of our cases showed defective development of the genitalia. In several you will have observed that the voice is rather high pitched and like that of a child. During growth the symptoms of testicular insufficiency usually are a feminine or childlike voice, non-growth of hair on the lip, chin, or pubes, the shoulders remain narrow, whereas the pelvis becomes broad, the legs are long, early obesity appears, the character fails to show, or loses energy and decision, and the epiphyseal cartilages do not ossify. After growth has been attained

the symptoms are essentially nutritional, terminating in obesity, loss of will, and muscular weakness. Increased testicular function at the time of puberty is characterized by excitement, over-activity, and irritability of the various psychic and somatic functions. Of course, we must ever associate the activity of the gonads with the other internal secreting glands.

A number of experimental investigations on the thymus gland have been carried out. Very young white mice and rabbits were injected with the blood-serum of full grown animals of the same species, with complete or nearly complete involution of the thymus. These injections were given for about eight days, and the animals were then killed after a varying length of time. Autopsy showed a distinctly lessened volume of the thymus, with more or less advanced histologic involution and delayed ossification, and, at the same time, a slight general body growth and diminished vivacity. Very young rabbits and dogs which were treated in the same way with blood serum of young animals with a normally functioning thymus presented a distinct increase in volume, with perfectly normal histologic behavior of the thymus, ossification and general body growth were above the normal and there was evident increased vivacity. All cases were controlled in non-injected animals in the same litter. The thymus, certainly in early life, appears to be a factor of influence upon osseous development. Two of the cases of dystrophy we had in this hospital have died. Autopsy was performed in one and the thymus was found to be in a state of subinvolution.





# CLINIC OF DR REUBEN OTTENBERG

## MOUNT SINAI HOSPITAL

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### A SURVEY OF THE HEMORRHAGIC DISEASES WITH ESPECIAL REFERENCE TO BLOOD FINDINGS<sup>1</sup>

Salient Points in the Clinical Classification of Hemophilia, Multiple Hereditary Telangiectases, Purpuras, and Hemorrhagic Disease of the Newborn Laboratory Findings in Hemorrhagic Diseases, Lesions of Blood-vessels, Coagulation Time, Physiology of Blood-clotting Infectious and Toxic Causes of Purpura. Application of Blood Findings in Diagnosis Three Simple Tests in Hemorrhagic Disease

**Introduction.**—The tendency to bleed was formerly called a diathesis. Within relatively recent years this vague "diathesis" has gradually emerged as a number of distinct conditions, some of them primary, so far as we can see, and some secondary to other disease. The pathogenesis of a few of them has become clear, and it is now possible to identify several by relatively simple laboratory findings. It is my purpose to present today the salient points in the clinical classification and to discuss those blood findings which are of value in diagnosis.

### HEMOPHILIA

As a result of the now universally accepted fact of prolonged blood-clotting and of the equally well ascertained and peculiar form of heredity, hemophilia has now been set off as an absolutely definite disease.

It is as much of a mistake to call anyone who shows a tendency to protracted bleeding a hemophilic as it would be to suppose that everyone who coughed was suffering from pneumonia.

<sup>1</sup>Clinical lecture delivered in the wards of Mount Sinai Hospital May 1918.

Hemophilia is a specific disease. It occurs only in males. There is some dispute about this latter point, but in all likelihood the English workers on heredity, Bulloch and Fildes, are right as to the "maleness" of hemophilia. The supposed cases of hemophilia in females reported in the literature were probably cases of chronic purpura.

From the clinical point of view hemophilia shows itself not by the tendency to bleed profusely, but by the tendency to keep on bleeding. No matter how minute a subcutaneous capillary is opened by some trivial trauma, it is likely to form a hematoma. The slightest abrasion of a mucous membrane may bleed for hours or days—may bleed till the patient dies. Repeated hemorrhages occur into the joints from the slight trauma incidental to ordinary muscular exertion, and most hemophiliacs who survive sooner or later become chronic cripples from this cause.

The immediate cause of this tendency to bleed is undoubtedly the failure of the blood to clot, or at least to clot within a reasonably short time. This failure or prolongation of clotting is practically pathognomonic of hemophilia. It is true that it may occur in a few other conditions, such as delayed chloroform-poisoning, phosphorus-poisoning, and melena neonatorum. But in these diseases it is a transient property, in hemophilia, a permanent characteristic of the blood of the individual.

Hemophilia is a hereditary disease, in fact, it is the hereditary disease par excellence. Nevertheless, sporadic cases do occur. But these are always males and are always characterized by prolonged blood-clotting. It is likely that all hemophiliac families start with such sporadic cases.

The hereditary transmission of hemophilia is often wrongly described, the disease is stated to be transmitted only by females. And, in fact, this generally is so, but not always, and not necessarily. For instance, look at Rebold's chart of five generations of a bleeder family (Table I, page 291).

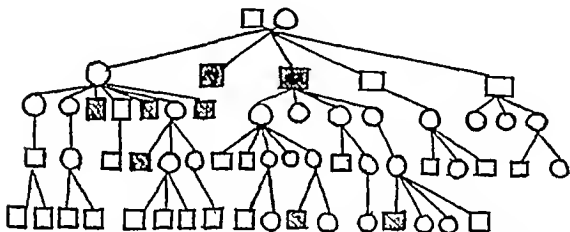
There is one instance in the chart where the disease, transmitted by a male, skips through two generations of females and reappears in the males of the last generation.

One is occasionally consulted by members of bleeder families

as to the advisability of marrying or having children Riebold's succinct four rules as to the heredity will help in formulating this advice They are

- 1 Hemophilia is active only in men, latent in women
  - 2 Latent mothers have some sons who inherit, some who do not, likewise daughters
  - 3 Descendants of healthy men of bleeder families are never bleeders
  - 4 The sons of bleeders are partly healthy, partly bleeders
- The daughters partly transmit the disease, partly not

TABLE I



Riebold's hemophilic family Squares indicate males circles indicate females shading indicates bleeders.

### MULTIPLE HEREDITARY TELANGIECTASES

A group of hereditary bleeders unique in its pathogenesis and different from hemophilia in every way has been separated largely by the efforts of Osler under the name of "multiple hereditary telangiectasis" The members of these families, at about the age of puberty, develop minute clusters of dilated venules in the skin and mucous membranes From these telangiectases exclusively they bleed, usually as the result of trauma. The hemorrhages in contradistinction to those of hemophilia are furious, but usually of short duration There are never ecchymoses or hemorrhages into joints such as occur frequently in hemophilia, and these individuals do not bleed more than normal from cuts and bruises The hemorrhages are never fatal except when they are from some

inaccessible mucous membrane The blood is normal in every way The disease affects both males and females and is transmitted by both, but it never skips generations Healthy members of the family have exclusively healthy descendants

### PURPURA

Aside from the two sharply defined types described above the vast number of other hemorrhagic conditions are not distinct disease entities Most of them can be, and generally are, spoken of as purpura In order to get a clear idea of the subject it is worth while to stop for a moment to analyze our conception of purpura and classify the clinical forms as well as we can with our present rather insufficient knowledge

Purpura, properly speaking, is a symptom and not a disease. The term applies to an acquired condition in which hemorrhages appear in the skin and mucous membranes In a very large number of instances the appearance of such hemorrhages is secondary to some other disease In a small group of cases no primary disease is known, and purpura here, for the present at any rate, may be regarded as a disease by itself

**Secondary Purpura.**—Purpura may be secondary to a vast number of other conditions which may be classified roughly under four heads

- 1 Infectious purpura
- 2 Purpura due to blood disease
- 3 Purpura due to toxic conditions
- 4 Purpura due to nutritional disturbance

### TABLE II

#### CLASSIFICATION OF CAUSES OF SECONDARY PURPURA

##### I *Acute Infections*

- 1 Of the newborn, including syphilis
- 2 General infections with staphylococcus or streptococcus
- 3 General infections with meningococcus or gonococcus.
- 4 Bacterial endocarditis
- 5 Exanthemata Small-pox, typhus, yellow fever, chicken-pox, measles
- 6 Diphtheria

II *Blood Diseases*

- 1 Aplastic anemia
- 2 Leukemia
- 3 Pernicious anemia

III. *Toxic Conditions.*

- 1 Affecting the liver chiefly
  - (a) Delayed chloroform-poisoning
  - (b) Phosphorus-poisoning
  - (c) Eclampsia.
  - (d) Prolonged jaundice.
  - (e) Peptone-poisoning (experimental)
  - (f) Cirrhosis of the liver
  - (g) Acute yellow atrophy of the liver
- 2 Affecting the bone-marrow chiefly
  - (a) Benzol poisoning
- 3 Mode of action unclassified
  - (a) Snake venom.
  - (b) Many drugs  
Potassium iodid mercury arsenic copaiba, quinin, ergot,  
belladonna.
  - (c) Anaphylaxis.

IV *Nutritional Disturbances and Other Causes*

- 1 Scurvy
- 2 Nephritis.
- 3 Tuberculosis.
- 4 Alcoholism
- 5 Old age
- 6 Cancer
- 7 Hodgkin's disease.
8. Mechanical purpura cardiac disease.
- 9 Nervous purpura

**Primary or Idiopathic Purpura** —These cases present a good deal of difficulty in classification. Several clinical forms have been described which seem so distinct as to constitute, in all likelihood, separate diseases. There are, however, occasionally intermediate forms, so that we are not yet sure whether idiopathic purpura constitutes one disease with various clinical manifestations, or several distinct diseases which may occasionally resemble each other more or less closely.

The most generally accepted clinical classification of idiopathic purpura is seen in Table III. I will take the forms up in the order in which they occur in this table.

## TABLE III

## CLASSIFICATION OF FORMS OF IDIOPATHIC PURPURA

- 1 *Simple Purpura*
  - (a) Acute
  - (b) Chronic.
- 2 *The Erythema Group*
  - (a) Arthritic purpura (Schönlein's disease or peliosis rheumatica)
  - (b) Visceral purpura (Henoch's purpura)
- 3 *Purpura Hemorrhagica* (morbus maculosus of Werlhof)
  - (a) Acute
  - (b) Fulminant.
  - (c) Chronic.
- 4 *Hemorrhagic Disease of the Newborn* (melena neonatorum)

1 **Simple Purpura (Purpura Simplex)**—This is a mild disease. Crops of purpuric spots, most commonly found on the lower extremities, are the only symptom the patient complains of, his health otherwise being perfect. There are no hemorrhages from mucous membranes and no arthritis. The disease often comes on in a short attack, from which recovery takes place in about two weeks. I have seen such a case with swelling of the spleen and a slight temperature rise.

There is another form, a chronic intermittent one, in which the patient is hardly ever free from a few purpuric spots, and at times exhibits a large number of them, and this in spite of otherwise perfect health. Both of these forms are more common in the young than in the aged, and in females than in males. The chronic form may persist for years. It is recognizable from the fact that aside from the typical petechiæ the patients usually notice that they bruise easily, so that at most times they can show a black-and-blue spot somewhere on the body.

2 **The Erythema Group**—(a) *Arthritic Purpura (Peliosis Rheumatica or Schönlein's Disease)*—This is sometimes incorrectly called purpura rheumatica. In this condition the purpuric manifestations are about the same as those in purpura simplex. In fact, Pratt proposes that the group be limited to cases of simple purpura associated with arthritis, such as the case originally described by Schönlein many years ago. Other authors include cases with hemorrhages from the mucous mem-

branes, and still others, Osler for instance, describe association of both the above with urticaria or erythema. At any rate, the striking thing is a complicating arthritis which may involve several joints and which is usually accompanied by some, though not very much, fever. Edema of the hands or feet sometimes occurs. The title "purpura rheumatica" ought to be dropped, because there is almost no evidence to connect this fairly distinct form of disease with true rheumatism. One reason for this belief is the failure of therapeutic effect of the salicylates. Also endocarditis and pericarditis are very rare in arthritic purpura, whereas they are common complications of true rheumatism. Furthermore, typical acute rheumatism practically never shows any tendency to purpura.



There is undoubtedly a close relationship between arthritic purpura and visceral purpura. In both of them the hemorrhagic features assume a relatively subordinate rôle. In both of them arthritis and various forms of urticaria and erythema occur. They are often classed together, according to Osler's suggestion, with angioneurotic edema and exudative erythema under the title of "the erythema group" or "the angioneurotic group." In neither of them does one see the diminished number of blood-platelets so characteristic of purpura hemorrhagica, the next form to be described. In fact, neither of them shows any characteristic blood changes. It is quite possible that these two forms belong by themselves and have no relationship to true purpura (purpura hemorrhagica) at all. The group of simple purpuras may merely represent mild or undeveloped cases belonging to one or the other of the two main groups of purpura.

### 3 Purpura Hemorrhagica (Morbus Maculosus of Werlhof)

—This is *par excellence* the form of purpura in which the hemorrhagic features predominate. The hemorrhages into the skin may be petechial, as in purpura simplex, or may be fairly extensive. Hemorrhages from the mucous membranes are the rule, epistaxis is the most frequent manifestation, and next to this in point of frequency comes menorrhagia, but hemorrhages may occur from the kidney, bladder, intestines, or, in fact, any of the mucous membranes. Arthritis is common. Nephritis and intestinal manifestations are evidenced at times, indicating a possible relationship of this form of purpura with that of Henoch. On the other hand, urticaria and erythema, which are found both in Henoch's purpura and in arthritic purpura, are very rare in purpura hemorrhagica. The disease may be acute or chronic.

The acute form is relatively infrequent. Ordinarily it is a serious disease lasting some weeks, but usually ending in complete recovery. The loss of blood is often large and may be alarming or even fatal. Superficially the hemorrhages bear considerable resemblance in character to those of hemophilia, the bleeding is slow but persistent and may occur from any minute lesion. Petechiæ as well as ecchymoses occur in both conditions. The

arthritis which occurs in a considerable proportion (about half) of the cases of purpura hemorrhagica is not always easy to distinguish from the joint hemorrhages of hemophilia. Nephritis and edema when they occur in purpura may aid diagnosis, but they only occur in a relative minority of the cases. In fact, there are so many points of resemblance that Frank applies the name pseudohemophilia to purpura hemorrhagica. And there is no doubt that before the introduction of the modern diagnostic criteria (coagulation time, bleeding time, and platelet count, which will be discussed a little later) many cases of purpura were mistaken for sporadic hemophilia and were so described.

There is a fulminant form which is one of the most terrible diseases known to medicine. The patient bleeds almost without cessation, the blood oozing from the various mucous membranes until death ensues, usually in a week or two. Several cases in the literature, and two in my own experience in which there was marked diminution or complete absence of polynuclear cells from the blood, suggest that this is a toxic condition in which the bone-marrow is directly attacked by some specific poison. This is plausible, particularly in view of Selling's work on benzol-poisoning, in which very similar clinical findings and pathologic pictures occur.

The chronic form of purpura hemorrhagica is more common than the acute. In fact, many authors, such as E. Frank and A. Miodet, believe that purpura hemorrhagica is always chronic, and that the cases which have been described as acute, with complete recovery, are simply those of individuals who have drifted out of sight before the recurrence, which these authors state may be delayed many months or even as much as nine or ten years.

4 Hemorrhagic Disease of the Newborn.—This is an important condition, and I discuss it along with purpura because it does not fit anywhere else, rather than because it is closely related to purpura. There is some doubt whether idiopathic hemorrhagic disease of the newborn deserves to be described as a separate clinical entity at all.

Among the newborn infants who bleed, one has to separate,

in the first place, those cases of true hereditary hemophilia. A large proportion of the deaths in hemophilia among the newborn are due to hemorrhage from the umbilicus or from circumcision. There are newborn infants which bleed from simple ulcers of the stomach or duodenum. Furthermore, one has to rule out cases of Winkel's disease, an acute epidemic infectious disease occurring chiefly in institutions and characterized by hemoglobinuria with icterus and cyanosis. A large number, perhaps the majority, of cases of severe purpura in the newborn are secondary to pyogenic infections or to syphilis. I have isolated staphylococci from the blood or found spirochetes in the liver of cases of this kind. Finally, eclampsia in the mother affects the infant in about half the cases and, besides liver degeneration, produces multiple thromboses and hemorrhages in various viscera.

Nevertheless, there are many cases of hemorrhage in the newborn for which no definite etiology can be assigned, and which for the time at least have to be classed as idiopathic. Those cases which show much fatty degeneration of the liver and other viscera at postmortem are often spoken of as Buhl's disease, an appellation which probably should be dropped, as the condition is not a distinct entity. Clinically, the cases resemble the very acute cases of purpura hemorrhagica. Bleeding from the stomach or intestines is most common, but the nose and other mucous membranes often bleed and purpuric spots and large subcutaneous hemorrhages occur, particularly about the head. On account of the predominance of gastro-intestinal bleeding the disease is often simply spoken of as *melena neonatorum*, but the gastro-intestinal hemorrhages are only an evidence of a general tendency to bleed. The mortality is high and the course is always short. The child invariably dies or gets completely well within one or, at most, two weeks.

The reports in the literature on the blood findings are contradictory. The few cases that I have had occasion to see have shown prolonged coagulation time. Icterus is usually present, and there are many reasons, which I have not time to go into here, for believing that the condition is really due to impairment of the liver functions.

## LABORATORY FINDINGS IN HEMORRHAGIC DISEASES

When one considers the wide variety of causes which may lead to secondary or symptomatic purpura (Table II), one sees that there is very little clue as to the etiology from a consideration of these causes. Infections, intoxications, disturbances of metabolism, and changes in the composition of the blood all play a rôle. Indeed, from the great variety of these causes one would conclude that purpura is a symptom called forth by so many different things that one could hardly expect for it a uniform pathogenesis. And such is, in all likelihood, the case. If the pathogenesis of secondary purpura, for which many causes are known, is obscure, one might expect this to be still more true of primary or idiopathic purpura for which no cause is known. And, indeed, this is so. There has been exceedingly little etiologic research on the primary purpuras, and we have little more than the surmise that some forms are infectious and others, such as the erythema group, toxic.

**Infectious and Toxic Theories**—Bacteriologic studies of all the different forms of purpura, other than those clearly secondary, have either been completely negative or have been so scattered and divergent in their results as to leave no doubt that the infectious agent, if such exists, must be one which eludes our present bacteriologic methods.

On the other hand, analogy with much experimental work in which many or most of the manifestations of purpura were produced by poisoning of various sorts, such as benzol, chloroform, diphtheria toxin, and certain kinds of sera, points to a toxic cause for the symptoms of purpura. If the causes are toxic, then, of course, the solution of the problem is simply moved one step further away and the sources of the toxic substances are to be sought.

**The Blood-vessels.**—Of the various ideas as to pathogenesis, the one which can be dealt with most briefly is the theory that the hemorrhages are due to degenerative lesions of the blood vessels. The attempt to actually demonstrate such lesions has, for the most part, been a failure, and the idea that toxic or infectious lesions of the capillaries are directly responsible for

the hemorrhages is generally based on analogy. Thus Gay and Southard were able to show that a form of fatty degeneration of the epithelium lining the capillaries may occur with astonishing rapidity in anaphylaxis, and it is well known that purpuric manifestations not infrequently occur in anaphylaxis when death does not supervene too quickly. Flexner likewise was able to show that snake venom, a substance which also produces symptoms of purpura, contains a poison, hemorrhagin, toxic to endothelial cells.

Certain facts in the clinical history of purpura also speak somewhat in favor of the vessel walls being weakened. Thus petechiæ and ecchymoses have a tendency to occur in dependent parts of the body or to be brought on by mechanical causes, such as rubbing, or stasis caused by a tight bandage, or coughing, or straining at stool. All of these point to possible, if not probable, weakness of blood-vessel walls.

Alfred F. Hess has recently taken advantage of this fact and has introduced a test for the resistance of the capillary walls. This test, which is known as the tourniquet test, was meant to be applied particularly in scurvy, but can be applied to other purpuric conditions as well. He found that whereas no petechiæ appeared in the skin of normal infants if a blood-pressure cuff was put around the arm and a pressure of 90 millimeters of mercury maintained for three minutes, the capillaries of infants suffering from scurvy gave way under this pressure and minute petechiæ were found on the arm. In adults a somewhat higher pressure has to be used, as the blood-pressure of adults is somewhat higher.

**Coagulation**—Most of the work on purpura of recent years has been on the subject of the blood rather than of the blood-vessels. Intensive study has been done on the physiology of blood-clotting. This was stimulated particularly by the discovery that in certain forms of hemorrhagic disease, notably hemophilia and the hemorrhages of the newborn, the clotting power of the blood was often greatly impaired, or even lost entirely. In spite of an enormous amount of work on the physiology of blood-clotting there is still a great deal to be learned

Simple as the process of the formation of a clot looks on analysis it turns out to be extraordinarily complex. Unfortunately, this complexity has led to very divergent views. In the maze of different terms and theories each one supported by plausible experiments it is hard to choose one's way. If we are to have any idea of the significance of the blood findings we must have some conception of the physiology of blood coagulation. There are certain broad outlines on which most of the experimenters are agreed.

1 The fibrin clot is formed out of a pre-existing dissolved protein, fibrinogen, present in the plasma of all animals. Fibrinogen is produced by the liver and a deficiency of it is the probable immediate cause of the hemorrhagic tendency in certain diseases of the liver such as acute yellow atrophy, cirrhosis of the liver, and yellow fever and in certain forms of poisoning such as phosphorus and chloroform.

2. The change of fibrinogen into fibrin is the result of the action of a substance called thrombin or fibrin ferment, which is not present in the circulating plasma but is formed at the time of clotting. It is always found in serum freshly expressed from a blood-clot. It is probably the thrombin in fresh serum that gives it its therapeutic value in checking hemorrhage. Thrombin deteriorates on standing. That is why serum used in treatment of hemorrhagic conditions should be fresh.

3 Thrombin is not present as such in the blood, but is formed from an antecedent substance known as prothrombin, present in the circulating plasma. The workers are not all agreed as to the properties of prothrombin. It is described in the literature under different names such as thrombogen (Morawitz), serozyme (Bordet and Delange), etc. It is thermolabile and deteriorates readily on standing. We are not absolutely certain as to whether it exists in the circulating plasma as such, or is given up to the plasma by the platelets as the initial act of clotting. Morawitz, Bayne-Jones, and others have shown that it can be derived from blood platelets.

4 Calcium in the ionic form is essential for the formation of clot, because without it prothrombin cannot be converted to

thrombin It must be exactly in the proper concentration An excess of calcium interferes with the formation of thrombin as much as does a deficiency There are a number of different theories as to what calcium does, but it must be confessed that its exact mode of action is at present a mystery The amount of calcium in plasma is so small that its measurement is not practical clinically Calcium deficiency has been reported in scattered instances of hemorrhagic disease, but in most of these the evidence is not very conclusive It does seem probable that the delayed coagulation and hemorrhagic tendency seen in obstructive jaundice are due to the blood calcium entering into some sort of combination with bile-pigments

Calcium salts, on the advice of Sir Almroth Wright, are much used in the treatment of hemorrhagic diseases There is much doubt at present as to their efficacy, particularly as in most cases the supposed calcium deficit, for which they are given, does not exist In giving calcium it is important to remember that an excess actually inhibits coagulation I believe I have seen this happen in a case of purpura

5 Thromboplastin is an important coagulation-accelerating substance which, like prothrombin, is derived from the blood-platelets and which, unfortunately, has received a great variety of names Alexander Smith, the first and greatest experimenter on the subject of blood coagulation, early recognized the existence of a thromboplastic substance, as he called it, and the most recent title for the substance, "thromboplastin," used by Howell and his followers, is perhaps the best one for it Other titles based on various views of its nature and origin are, however, frequently used in the literature Thus Morawitz's term "thrombokinas" is based on his view that the substance acts in a manner analogous to the kinases of digestive enzymes, Bordet and Delange use the name "cytozyme," since they believe that the substance is particularly derived from cellular elements in contrast to prothrombin, which they call "serozyme," because they believe it to be present in solution Nolf uses the term "thrombozyme" for the same substance

This substance, for which we shall use the term "thromboplastin," is undoubtedly derived from blood platelets at the time of coagulation, and in all likelihood it cannot be derived from red blood-cells or leukocytes. A substance identical or having closely similar properties can be obtained by making extracts of many different kinds of body tissues. It has been shown by Zak, Bordet and Delange, Howell, and others that thromboplastin is a lipin, very likely a lecithin or cephalin, since it is soluble in alcohol and ether, but not in acetone. There is very great divergence of opinion as to how thromboplastin works. Morawitz, Mellanby, and many others believe that it is an essential element for coagulation and enters into the actual formation of thrombin, uniting with prothrombin for that purpose. Howell and his school believe that its action is entirely different, and that it simply neutralizes an inhibiting substance, anti-thrombin, present in all plasma, and in this way permits coagulation to go on. They base their view to some extent on the fact that thromboplastin accelerates clotting especially in those plasmas known to contain large amounts of anti-thrombin, such as the plasma of birds, peptone plasma, and hirudin plasma.

A deficiency of thromboplastin either in the blood or the tissues has been asserted for various hemorrhagic conditions, but especially and with considerable show of reason for hemophilia. There are absolutely contradictory opinions on this question, and I do not wish to enter the controversy here. But, at any rate, the enormous accelerating effect of tissue extracts and of platelet extracts on the coagulation of the blood of hemophiliacs is very easy to demonstrate.

Thromboplastin has acquired important therapeutic uses. It is one of the most valuable local hemostatics we possess. It is applied in several forms either as extracts of various tissues, such as brain or lung, under the names of thromboplastin or thrombokinas, or as an extract of blood platelets (coagulen of Kocher and Fonio), or by the direct application of fresh or living tissues (Victor Horsley). The possibility of this last application is worth remembering for emergencies when the

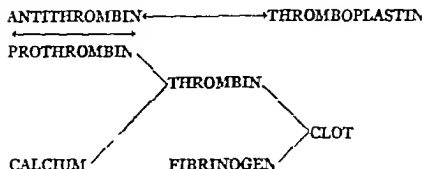


prepared extracts are not at hand. The intravenous use of thromboplastin chiefly in the form of platelet extract has been proposed, but must be carried out very cautiously, as the substance is very toxic when given in this way. Coagulen, however, can safely be given subcutaneously, but we do not as yet know much about its effects after absorption.

6 Not the least important of the substances which enter into the process of coagulation is antithrombin. This is undoubtedly present in normal circulating plasma. It is probably necessarily there in order to prevent excessive intravascular clotting. From the property which clotted blood has of liberating thrombin, and the power which thrombin has of forming more clot from fibrinogen, one can see that if there were not some hindering factor present, a clot once started at any point in the circulatory system would grow by accretion until it filled the entire system. As with the other substances, there is a good deal of divergence of opinion as to just what antithrombin does, whether it antagonizes the action of thrombin when once formed, or prevents the formation of thrombin from prothrombin. The latter view is that of Howell and is now most generally accepted. Howell's view of the interaction of these substances is that prothrombin is capable of forming thrombin spontaneously in the presence of calcium, but that prothrombin is constantly prevented from doing this in the circulating blood by the presence of antithrombin.

Prothrombin and antithrombin are thus always in a delicate balance, the one against the other. The only function of thromboplastin (a function by which it virtually, under normal conditions, initiates coagulation) is to combine with antithrombin, thus freeing the prothrombin so that it can form thrombin. Complicated as this theory sounds, there is good experimental evidence supporting it. The exact chemical nature of none of the substances involved is known, although thrombin has been obtained in a relatively pure condition by Howell. Whipple's diagram (Table IV) to illustrate Howell's theory will help to keep in mind how these substances interact.

TABLE IV



Antithrombin is very resistant to heat, as compared with prothrombin and fibrinogen, and on this property is based the test for its presence recently proposed for clinical use (Howell, Whipple, Hess)

Antithrombin, like fibrinogen, is believed to be produced by the liver, and the amount in the blood is increased automatically as a reaction to the presence of various substances which injure the liver or accelerate blood coagulation, such as peptone, serum, and the products of cell disintegration. A pathologic increase of antithrombin has been claimed for many hemorrhagic conditions. Whipple seems to have proved it in purpuras secondary to carcinoma of the liver, miliary tuberculosis, aplastic anemia, and leukemia. He points out that in cases of hemorrhage known to be due to antithrombin increase, serum treatment may do more harm than good, as it is known to reactively lead to the increase of antithrombin in the body. In these cases especially blood transfusion is indicated.

#### APPLICATION OF BLOOD FINDINGS IN DIAGNOSIS

The intensive study of these various factors of blood coagulation is ultimately bound to be of the greatest importance, and to throw much light on the causes and treatment of the hemorrhagic diseases. Their detailed study, however, has little more than begun. At present in practical diagnosis certain simple tests are of much greater importance, and give much more definite results. I will discuss three of these in detail. With the aid of these three tests alone it is possible to classify a considerable proportion of the hemorrhagic diseases (Table V)

TABLE V

## BLOOD DIAGNOSIS OF FORMS OF HEMORRHAGIC DISEASE

	Blood coagulation.	Bleeding time.	Blood platelets
Hemophilia	Enormously prolonged	Normal or prolonged	Normal
Hemorrhage of the newborn	Greatly prolonged	Prolonged	
Purpura hemorrhagica	Normal	Greatly prolonged	Greatly decreased
Purpura secondary to—			
1 Jaundice	Prolonged.	Prolonged	Normal
2 Chloroform or phosphorus	Prolonged	Normal	
3 Scurvy	Normal	Normal	Normal
Purpura simplex			
Arthritic purpura			
Visceral purpura			

1 The Coagulation Time of the Blood — This is perhaps the most important of all tests in hemorrhagic disease. Innumerable methods have been proposed for determining the coagulation time. The more recent studies on the coagulative properties of tissue fluids have shown that most of the coagulation time methods in the text-books and the literature are valueless. We now know that the only methods on which much reliance can be placed are those in which the blood is obtained directly from a vein through a hollow needle. The coagulation time is greatly affected by the amount of blood withdrawn. Large amounts always take a longer time to clot than small ones because clotting is initiated by some change that occurs at the surface of contact of the blood with a foreign body.

For practical purposes the simplest and most reliable method of determining blood coagulation time, therefore, is to apply a tourniquet to the arm, to insert a fairly good-sized hollow needle directly into an arm vein, and collect 2 or 3 c.c. of blood in a perfectly clean smooth test-tube. This should be placed in a

glass of water at approximately body temperature, as lower temperatures have a retarding influence on coagulation. Coagulation can be judged by tilting the test tube from time to time. Beginning coagulation is shown by the adherence of the blood to the glass, full coagulation is shown by the clot retaining a firm form even when the tube is inverted. Normal coagulation time by this method varies from five to ten minutes.

When coagulation time is tested by obtaining drops of blood from a prick of a finger or the ear lobe, the coagulation time is always shorter than when the blood is obtained from a vein. I have seen a case of hemophilia in which the blood that came from a vein required one and a half hours to clot, and blood obtained from the finger tip clotted in seven minutes. On the other hand, in cases of extreme prolongation of coagulation time one usually gets prolongation also in the coagulation of blood obtained from the finger-tip. In fact, in a case of hemorrhage of the newborn, I have seen blood from a needle prick of the heel fail to coagulate at all. Since, however, the coagulation time of blood so obtained generally varies simply in proportion to the amount of tissue fluid that happens to be expressed with the blood, the method should be discarded.

For the same reason, when blood is obtained from a vein through a hollow needle, it is important that the needle go directly into the vein. If the needle fails to strike the vein at once, it is better to withdraw it and try again with a fresh needle.

Prolonged coagulation time is characteristic, above all, of true hemophilia, either hereditary or sporadic. It occurs also in the hemorrhagic disease of the newborn, and in some forms of secondary purpura, particularly in those in which the liver parenchyma is greatly damaged, as in chloroform- and phosphorus-poisoning. On the other hand, the coagulation time of the blood is normal or only very slightly prolonged in all forms of idiopathic purpura and in most forms of secondary purpura.

The cause of delayed coagulation undoubtedly differs in different cases. In hemophilia the consensus of more recent opinions is that there is a deficiency in amount or in quality

of prothrombin, but there is a considerable school of important workers, such as Morawitz, Sahl, Fuld, and Mellanby, who believe that the deficiency is chiefly in thromboplastin, generally called by them thrombokinas. On the other hand, in hemorrhagic disease of the newborn and in chloroform-poisoning the prolonged coagulation is due to a deficiency of fibrinogen.

The one important outstanding fact to remember about the coagulation time is the ease with which hemophilia can be distinguished from purpura by determining it. Particularly in distinguishing cases of chronic purpura from hemophilia it is of real diagnostic value.

2 Bleeding Time From Small Pricks or Cuts—In 1910 W. W. Duke pointed out that patients with purpura hemorrhagica continued to bleed from small needle pricks in the skin for a much longer time than normal people. This phenomenon had been observed in scattered cases by many others, but, due to Duke's painstaking observations, the simple test of bleeding time has become one of great clinical value. The size and depth of the needle cut do not affect the bleeding time very greatly, but it is important not to massage the part or to exert pressure in wiping away the drops of blood, as the forcing of much tissue fluid into the cut shortens the bleeding time considerably.

The technic of the test consists of making a prick, preferably on the lobe of the ear, because the skin there is generally of uniform thickness, and wiping away the drops of blood that exude with a piece of blotting-paper every half-minute. It is important to wipe all of the drop away completely, because if any blood is allowed to remain on the outside of the cut it may clot and shorten bleeding time. I have a preference for absorbent cotton instead of the blotting-paper because it removes the drops of blood more neatly. In normal individuals the bleeding stops in from two and a half to five minutes, where blotting-paper is used five to ten drops can be counted. In purpura hemorrhagica, both *primary* and *secondary*, and in hemorrhagic disease of the newborn the bleeding time is greatly prolonged and may last for hours. On the other hand, in hemophilia it is not, as a rule, greatly prolonged, though it is so

occasionally. In *purpura simplex*, *arthritic purpura* and *vascular purpura*, and in *scurvy* the bleeding time is normal. I will discuss the cause of prolonged bleeding time in *purpura hemorrhagica* under the next heading blood-platelets.

3 The Count of Blood-platelets.—The great importance of the blood-platelets in coagulation is apparent from all I have said. These little bodies so inconspicuous that for years their importance was overlooked, certainly give rise to thromboplastin and probably to prothrombin. The reason for the curious incoagulability of a bird's blood, if carefully removed through a cannula, is that it contains no platelets and only gets its thromboplastin from the tissues, in contact with which it coagulates with great rapidity.

Besides this, it has been known for years that agglutinated platelets form the great part of occlusive thrombi, and in this way play a direct rôle in stopping hemorrhage. Probably due to their sticky surface, they adhere to the newly laid down fibrin to a much greater extent than do leukocytes or red blood-cells. This is why the cross-section of a thrombus looks so different from the cross-section of a blood-clot. Besides this it has been asserted that platelets are responsible for the contraction of blood-clot and the exudation of serum from it. And it is widely asserted that failure of the blood-clot to retract is characteristic of *purpura*. I have been unable to confirm this observation. The failure of retraction seems to be an accidental occurrence, I have repeatedly seen it in normal blood. Furthermore, retraction is a characteristic of all clotted colloids (gels). Besides this, it is hard to see how clot retraction could play an important rôle in the stoppage of hemorrhage, one would expect rather the reverse.

The remarkable reduction in the number of platelets in *purpura hemorrhagica* was discovered by Denys, a Belgian, in 1887, only five years after the discovery of the platelets themselves by Bizzozero in 1882. Denys's finding was confirmed by Havem in 1895. But until recent years it has not received the attention in diagnosis that it deserves. This has been due chiefly to the somewhat difficult methods in vogue for counting the blood-

platelets The great value of the platelet count in differentiating the cases of hemorrhagic disease has more recently been confirmed and accentuated by W W Duke, and subsequently by many others He pointed out that the common feature in a considerable variety of diseases in which purpura hemorrhagica occurs as a complication is the reduction of the number of platelets in the blood He found that this was the pathologic feature that united the cases of secondary purpura hemorrhagica with the idiopathic cases He says "Purpura hemorrhagica of the type described would seem, therefore, a symptom, not a disease It is caused apparently by any agent which reduces the platelet count to a sufficient degree" In his cases, which included not only cases of idiopathic purpura but also of purpura secondary to other diseases, the number of platelets per cubic millimeter did not exceed 10,000 Furthermore, various other writers, such as Selling, with the use of benzol as a poison, Le Sourd and Pagniez, and Watabiki, by the use of sera which agglutinated or dissolved platelets, were able to produce purpura experimentally and to demonstrate the reduction in the number of platelets

In practical work, therefore, the platelet count is a thing of real value and importance It can be done with sufficient accuracy by a simplified method, which was described in a publication by N Rosenthal and myself, by which one is enabled to count the red blood-cells at the same time The method consists of the use of 3 per cent sodium citrate as a diluting fluid The blood is diluted in the red cell counting pipet of the hemocytometer exactly as though red cells alone were going to be counted The blood must be allowed to stand in the counting chamber for ten minutes at least in order that the blood-platelets, which are of relatively low specific gravity, may have time to settle down to the surface of the ruled squares They are then counted in the same manner as red blood-cells, except that on account of their relative scarcity about ten times as many squares ought to be counted With a little practice there is no difficulty in identifying the platelets A high-power dry lens should be used There are several other methods almost equally easy which give satisfactory results, and the performance of a platelet count need

not add more than ten minutes to the time taken for the performance of a routine blood count. The normal number of platelets varies from 200,000 to 400,000 per cubic millimeter. Reductions below 50,000 are practically always accompanied by purpura.

The connection between deficient blood platelets and purpura is not entirely easy to make out. If, as the experimental work seems to show, the blood platelets are the source of most of the essential substances which go to form thrombin, it is hard to understand why in purpura the blood removed from the vessels clots in normal time in spite of deficient blood platelets. Hess has recently suggested that the substance of the blood platelets is simply dissolved in the blood-plasma, the platelets, as such, not being present. Even this does not completely answer the question, because if the dissolved constituents of the platelets are present, it is hard to see why they do not show their characteristic effects in checking bleeding.

Recent work by a number of observers in an entirely different field, notably by Janeway, Richardson and Park, has probably solved this riddle. In seeking for an explanation for the well known vasoconstricting action of the blood serum, formerly erroneously attributed to adrenalin in the blood, these workers discovered that the vasoconstricting substance is derived exclusively from the blood platelets, it is not present in plasma free of blood platelets. This seems to offer at once a very neat explanation of the otherwise contradictory fact that in purpura bleeding from small cuts continues for an enormously prolonged time in spite of the fact that the blood clots normally. The constriction of the opened capillaries and small vessels by the action of the vasoconstricting substance of platelets plays a great rôle in the normal stoppage of capillary bleeding. It is easy to see that the absence of this vasoconstricting substance may cause almost indefinite prolongation of hemorrhage from cut vessels.





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American Journal of Medical Sciences

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